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663. *The Constitution of Laminarin. Part III.* The Fine Structure of Insoluble Laminarin.*

By F. B. Anderson, E. L. Hirst, D. J. Manners, and A. G. Ross.

Insoluble laminarin, a mixture of glucans isolated from *Laminaria cloustoni*, has been investigated by periodate oxidation and methylation. The presence of mannitol (2%) has been confirmed, and approximately half the molecules are terminated by a mannitol residue. Some of the molecules have a low degree of branching, and the constituent chains appear to be interlinked by β-1 : 6-glucosidic linkages. Many of the branched molecules contain mannitol.

The polysaccharide material isolated after the reduction of laminarin with potassium borohydride, and after treatment with lime-water, has also been examined; their structures support the above conclusions on the fine structure of laminarin.

The molecular structure of laminarin, a mixture of glucans which form a reserve carbohydrate in various species of brown marine algae (Phaeophyceae), has been the subject of several recent investigations. The material exists in two forms which differ in solubility in cold water. A "soluble" form is present mainly in *Laminaria digitata*, whilst "insoluble" laminarin has been isolated from the fronds of a number of species of Laminariaceae. The present paper is concerned only with the laminarin from *L. cloustoni*.

Methylation studies carried out by Barry [1] showed that insoluble laminarin was composed of β-1 : 3-linked D-glucopyranose residues, whilst successive oxidation with periodate and bromine indicated [2] an apparent chain length of sixteen glucose residues. However, a later investigation (Part I [3]) suggested that laminarin was composed of about twenty β-1 : 3-linked glucose residues, although the reducing power was unexpectedly low. It was concluded [3] that a proportion of the reducing glucose groups were in some way modified. A similar investigation of soluble laminarin from *L. digitata* was described in Part II [4] and will be considered in detail in a later communication.

An important development in laminarin chemistry was the discovery that mannitol (*ca.* 2%) was a constituent residue.[5] After partial acid hydrolysis of laminarin, Peat, Whelan, and Lawley separated from the mixed saccharides small quantities of mannitol, 1-*O*-β-D-glucosylmannitol and 1-*O*-laminaribiosylmannitol in addition to much larger amounts of glucose, laminaribiose, and higher laminarisaccharides. This finding, together with other evidence, showed that a *proportion* of the molecules were terminated by a mannitol residue linked through one of the two primary alcohol groups. A further discovery, which suggested that laminarin contained a few β-1 : 6-glucosidic linkages, was the isolation of a small quantity (0·26%) of gentiobiose, together with two isomeric trisaccharides, 6-*O*-β-laminaribiosylglucose and 3-*O*-β-gentiobiosylglucose. Since Peat and his co-workers considered that positive evidence for branching was not available (a significant quantity of 3 : 6-di-*O*-β-glucosylglucose could not be isolated), they suggested that one of the possible structures for laminarin was "a linear molecule of β-glucose residues in which repeating sequences of 1 : 3-links are occasionally interrupted by a 1 : 6-linkage." We are indebted to Professor Peat and Dr. Whelan who kindly allowed us to see two papers [5] before publication.

The present communication describes further methylation and periodate oxidation

* Part I, *J.*, 1950, 3494; Part II, *J.*, 1951, 720.

[1] Barry, *Sci. Proc. Roy. Dublin Soc.*, 1939, **22**, 59.
[2] Barry, *J.*, 1942, 578.
[3] Connell, Hirst, and Percival, *J.*, 1950, 3494.
[4] Percival and Ross, *J.*, 1951, 720.
[5] Peat, Whelan, and Lawley, *Chem. and Ind.*, 1955, 35; Peat, Whelan, Lawley, and Evans, *Biochem. J.*, 1955, **61**, x; Peat, Whelan, and Lawley, *Proc. Chem. Soc.*, 1957, 340; *J.*, 1958, 724, 729.

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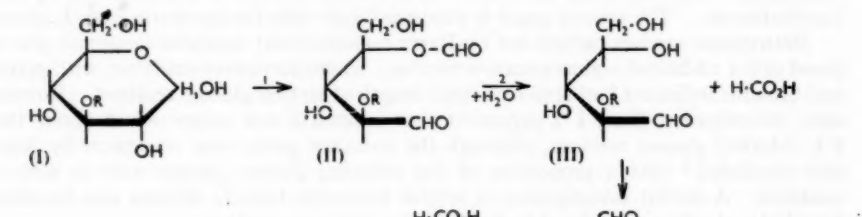
studies of insoluble laminarin. Degradation of laminarin by lime-water has also been examined. A preliminary account of part of this work has appeared elsewhere.[6] The following abbreviations are here used: average chain length ($\overline{CL}$) denotes the average number of residues per non-reducing glucose end-group; degree of polymerisation ($\overline{DP}$) refers to the average number of residues per molecule. Chains terminated at the reducing end by glucose or mannitol are described as G-chains or M-chains, respectively.

Isolation and Properties of Laminarin.—The laminarin was one sample, prepared by Dr. W. A. P. Black. It was extracted from the seaweed at 55° with dilute hydrochloric acid (pH 3·4) in 1 hr. and when purified had a glucose content of 94%, $[\alpha]_D$ −9° in H_2O, +9° in N-sodium hydroxide, and contained one reducing group per 47 residues (hypoiodite oxidation). (The insoluble laminarin examined in Parts I[3] and II[4] had reducing powers corresponding to one reducing group per 40 and 45 residues respectively.)

A partial acid hydrolysate was shown by paper chromatography to contain glucose, laminaribiose, laminaritriose, and unidentified sugars with $R_{Glucose}$ values of 0·45 (non-reducing), 0·34, 0·24, and 0·16. A complete acid hydrolysate contained mannitol. Since D-glucose and mannitol have similar R_G values in the usual paper chromatographic solvents, two different experiments were carried out. In the first, the glucose was converted into the less mobile D-gluconic acid by addition of D-glucose oxidase[7] to the neutralised hydrolysate. A non-reducing carbohydrate with the R_G value of mannitol was then revealed.



The presence of mannitol (and a non-reducing disaccharide) has also been shown by using a special solvent (ethyl methyl ketone–acetic acid–water, saturated with boric acid) kindly communicated by Dr. W. R. Rees.

Periodate Oxidation Studies.—Periodate oxidation[8] of a 3-*O*-substituted glucose (I) may involve at least three reactions: (1) normal Malapradian oxidation of α-glycol groups, (2) slow hydrolysis of a formyl ester (II), followed by further Malapradian oxidation, and (3) oxidation of an activated hydrogen atom in a structure (V) of malondialdehyde type. In contrast, periodate oxidation of 3- or 6-*O*-substituted hexitols (VII and VIII) requires

[6] Anderson, Hirst, and Manners, *Chem. and Ind.*, 1957, 1178.
[7] Keilin and Hartree, *Biochem. J.*, 1948, **42**, 230.
[8] For a review, see Bobbit, *Adv. Carbohydrate Chem.*, 1956, **11**, 1.

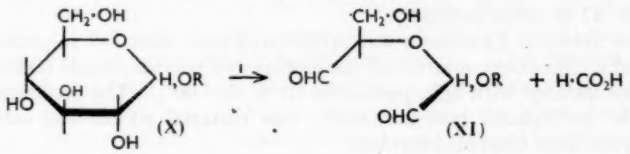
only normal Malapradian-type reactions to yield respectively the malondialdehyde derivative (V) or the substituted acetaldehyde derivative (IX):

$$\underset{\text{(VIII)}}{RO{\cdot}CH_2{\cdot}[CH(OH)]_4{\cdot}CH_2{\cdot}OH} \xrightarrow{I} \underset{\text{(IX)}}{RO{\cdot}CH_2{\cdot}CHO} + 3H{\cdot}CO_2H + H{\cdot}CHO$$

Partial acid hydrolysis [5] and methylation [1,3] indicate that in laminarin the chains are terminated at the potential reducing end by either a reducing glucose residue linked at $C_{(3)}$ or a mannitol group, as represented in formulæ (I) and (VIII) respectively (where R is a chain of β-1 : 3-linked glucose residues).

Oxidation of non-reducing end-groups (X) also proceeds without a formyl-ester intermediate, to give the stable dialdehyde (XI).

The relative rates of these reactions have been controlled by using three oxidation conditions: (*a*) Initial primary oxidation (I ⟶ II, VII ⟶ V, VIII ⟶ IX, and X ⟶ XI) by sodium metaperiodate at 2°, whereby the rate of hydrolysis of formyl esters is greatly reduced,[9] (*b*) total primary oxidation (I ⟶ V, and normal oxidation of VII, VIII, and X) with potassium metaperiodate [10] or a limited excess of sodium metaperiodate [11] at room temperature, and (*c*) sodium metaperiodate buffered at pH 8 at room temperature, enabling reactions (1), (2), and (3) to take place.[12]



Control experiments have shown that the initial primary oxidation of laminaribiose (giving structures II and XI) required some 14 hr., and that formaldehyde production from this sugar, or from 3-*O*-methyl-D-glucose, was not observed until after 3 days' oxidation. In contrast, the oxidation of laminarin under similar conditions gave formaldehyde within 1 hr. This observation is not only consistent with the presence of terminal-mannitol residues, but also provides a method of estimation. The initial yield * of formaldehyde (0·02 mol.) is equivalent to the presence of 2% of mannitol in the laminarin.

Measurements of the formaldehyde liberated during the total primary oxidation of laminarin and the corresponding alcohol (laminaritol) have been used to determine the number average $\overline{DP}$ and the proportion of M-chains. This oxidation (with a limited excess of sodium metaperiodate at room temperature) gave 0·041 mol. of formaldehyde from laminarin. Since the oxidation of either G- or M-chains gives rise to one mol. of formaldehyde per chain, this value corresponds to a $\overline{DP}$ of 24. After reduction of laminarin with potassium borohydride (p. 3237) the laminaritol so produced yielded 0·063 mol. of formaldehyde on similar oxidation. It follows that 0·022 mol. of formaldehyde arises from the G-chains in laminarin, and that the remaining 0·019 mol. is liberated from M-chains. Calculations from these data show that the laminarin sample of $\overline{DP}$ 24 contains (*a*) 46% of M-chains, (*b*) 1·9% of mannitol, and (*c*) one reducing group per 45 glucose residues.

During the oxidation of laminarin at pH 8, only the residues (VIII) and (X) of the M-chains will be attacked, whilst linear G-chains will be degraded in stepwise fashion with the production of one mol. of formaldehyde per glucose residue. This oxidation process is

* The products liberated on periodate oxidation are normally reported as mol. per anhydrohexose residue.

[9] Meyer and Rathgeb, *Helv. Chim. Acta*, 1948, **31**, 1540; 1949, **32**, 1102.
[10] Halsall, Hirst, and Jones, *J.*, 1947, 1427.
[11] Manners and Archibald, *J.*, 1957, 2205.
[12] Hough and Perry, *Chem. and Ind.*, 1956, 768.

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inhibited by 1 : 6-linkages since these, like the mannitol residue, give rise to stable acetaldehyde derivatives (IX).[12] Our laminarin sample gave 0·52 mol. of formaldehyde, a value similar to that reported by Hough and Perry.[12] This result is in good agreement with that expected for a laminarin containing approximately equal numbers of M- and G-chains, many of the latter being linear.

The $\overline{CL}$ of laminarin can be deduced from the amount of formic acid produced during the initial primary oxidation. The observed figure, after 6 hours' oxidation with potassium metaperiodate at room temperature, or 24 hours' oxidation with sodium metaperiodate at 2° (see p. 3242), is 0·10 mol., *i.e.*, 10 mol. of formic acid per 100 hexose residues. Since each mannitol residue gives rise to 3 mol. of formic acid, 5·7 mol. will originate from these, and the remainder (4·3 mol.) must arise from non-reducing end-groups. The proportion of these is therefore one per 23 glucose residues. In view of later evidence of heterogeneity, this numerical agreement between the $\overline{DP}$ and $\overline{CL}$ values is considered to be fortuitous, and not an indication of a linear structure.

The proportion of free reducing groups in the polysaccharide may be estimated from the rate of production of formic acid. As stated above, the initial primary oxidation yields 0·10 mol. whereas the total oxidation [after the hydrolysis of formyl ester groups (II) which requires 8—10 days] gives 0·15 mol. Since 0·05 mol. of formic acid is liberated from reducing glucose end-groups, the proportion of these is one per 40 glucose residues (cf. one per 45—47 by other methods).

Methylation Studies.—Laminarin was methylated with dimethyl sulphate and sodium hydroxide, and a chloroform solution of the methylated polysaccharide (OMe, 44·0%) was fractionally precipitated with light petroleum (b. p. 40—60°). The precipitate amounted to 78% of the methylated polysaccharide; the material which was soluble in light petroleum has not been examined further.

Hydrolysis of insoluble methylated laminarin gave 2 : 3 : 4 : 6-tetra- (4·4%), 2 : 4 : 6-tri- (84·6%), 4 : 6-di- (1·9%), unidentified di- (7·2%), and mono-*O*-methyl-D-glucose (1·9%). The proportion of tetra-*O*-methylglucose is equivalent to a $\overline{CL}$ value of 23 (not 20 as stated in ref. 13). No tri-*O*-methylglucose other than the 2 : 4 : 6-isomer could be detected.

The molecular weights of the whole and of insoluble methylated laminarin, as determined by isothermal distillation,[13] were respectively 1900 and 12,000, equivalent to $\overline{DP}$ values of 9 and 58. It follows that the material (22%) soluble in light petroleum had a molecular weight of *ca.* 500 ($\overline{DP}$ 2—3).

Although the measurement of molecular weights in the range 2000—20,000 is extremely difficult, the isothermal distillation measurements (which in this range are accurate to within 10%) show that the $\overline{DP}$ of methylated laminarin is much larger than the $\overline{CL}$, and a number of the molecules must therefore contain a small number of branch points. On the average, two branch points per molecule appear to be present. Evidence on the nature of the interchain linkage has not been obtained from the methylation analysis since undermethylation of the polysaccharide and hydrolytic demethylation of 2 : 4 : 6-tri-*O*-methylglucose [3,4] both give rise to di-*O*-methylglucose. However, the presence of oligosaccharides containing β-1 : 6-glucosidic linkages in partial hydrolysates of laminarin [5] suggests that these are, in fact, present as interchain linkages. These would number only 2—3% of the total glucosidic linkages, in agreement with the small observed yield of gentiobiose. The failure to isolate 3 : 6-di-*O*-β-glucosylglucose from a partial hydrolysate is not inconsistent with this view. In analogous experiments with other branched polysaccharides, hydrolysis of glycosidic linkages adjacent to interchain linkages does not appear to be random. Thus, the major trisaccharide containing an interchain linkage in a partial hydrolysate of glycogen or amylopectin is panose;[14] significant quantities of 4 : 6-di-*O*-α-glucosylglucose have not been isolated.

[12] Broatch and Greenwood, *Chem. and Ind.*, 1956, 1015.
[14] Peat, Whelan, and Edwards, *J.*, 1955, 355; Thompson and Wolfrom, *J. Amer. Chem. Soc.*, 1951, **73**, 5849.

Degradation of Laminarin with Lime-water.—The susceptibility of reducing glucosaccharides and, in particular, laminarin to degradation by aqueous alkali is well known (see, for example, Part II [4]). Recent studies by Corbett and Kenner [15] showed that insoluble laminarin, on prolonged treatment with oxygen-free lime-water at 25°, is degraded in stepwise fashion from the reducing group to give D-glucometasaccharinic acid in 40—50% yield. Termination of the reaction was ascribed " to some inhibitive variation in chain structure " and Corbett and Kenner pointed out that degradation by lime-water would cease when 1 : 6-linkages were encountered in the molecule. It is now clear, however, that the degradative action of lime-water must be confined to the G-chains, and in laminarin samples containing an appreciable number of M-chains incomplete conversion into D-glucometasaccharinic acid is to be expected.

We carried out similar experiments, but at 60°, and subjected the residual polysaccharide to methylation analysis. Laminarin was treated with oxygen-free lime-water for 23 hr. at 60°. Unattacked polysaccharide which separated was collected (46% recovery). Re-treatment of this material with lime-water did not cause any appreciable degradation, so that more than 50% of the laminarin had been transformed into soluble products. The lime-treated laminarin had $[\alpha]_D^{20}$ −7° (in H_2O), only a very slight reducing power, and contained mannitol. On partial hydrolysis with oxalic acid, a series of oligosaccharides similar to those in the laminarin hydrolysate (p. 3234) were obtained.

Methylated lime-treated laminarin was prepared (OMe, 44·1%) and fractionated with light petroleum. It proved to be more homogeneous than the methyl ether of laminarin as 88% of the material was insoluble in light petroleum. This fraction, which had a molecular weight of 13,600 by isothermal distillation [13] (equivalent to $\overline{DP}$ 65), will be referred to as " methylated lime-treated laminarin." Since the whole methylated sample had a molecular weight of 2500, the material (12%) soluble in light petroleum consisted of methylated saccharides of $\overline{DP}$ *ca.* 2.

An acid hydrolysate of " methylated lime-treated laminarin " (see above) contained the following sugars: 2 : 3 : 4 : 6-tetra- (5·2%), 2 : 4 : 6-tri- (84·4%), 4 : 6-di- (1·5%), unidentified * di- (7·2%) and mono-*O*-methyl-D-glucose (1·8%). These proportions are generally similar to those present in the hydrolysate of methylated laminarin (p. 3236). The " methylated lime-treated laminarin," like methylated laminarin, thus contains molecules with a low degree of branching, namely, an average of two branch points per molecule.

The sedimentation of lime-treated laminarin in the ultracentrifuge has been compared, by Broatch and Greenwood,[13] with that of the original polysaccharide. The insoluble laminarin was extremely heterogeneous and had a sedimentation constant of $0{\cdot}5 \times 10^{-13}$ c.g.s. units, whereas the lime-treated material was more homogeneous and had a much larger sedimentation constant ($1{\cdot}0 \times 10^{-13}$ c.g.s. units). These results indicate that the lime-water treatment has preferentially degraded the polysaccharide material of low molecular weight. This degradation is confined to G-chains, and many of the molecules of higher molecular weight (branched) must therefore be terminated by mannitol residues.

Preparation and Methylation of Laminaritol.—Free reducing groups in a polysaccharide can be reduced to the corresponding alcohol residue. The conversion of laminarin into laminaritol (with G-chains terminated as in VII) was first reported by Abdel-Akher, Hamilton, and Smith [16] who used sodium borohydride as reducing agent. With potassium borohydride, we have prepared laminaritol which was virtually non-reducing, with $[\alpha]_D$ −8° (in H_2O) and a glucose content of 94%.

* *Added May 10th, 1958*: This di-*O*-methyl sugar has now been identified as the 2 : 4-isomer since it could be differentiated from 2 : 6- and 4 : 6-di-*O*-methylglucose by paper electrophoresis, and on periodate oxidation formaldehyde was liberated. This finding is in accord with, but not proof of, a branched structure.

[15] Corbett and Kenner, *J.*, 1955, 1431.
[16] Abdel-Akher, Hamilton, and Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 4691.

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If our previous deductions on the structure of laminarin and its periodate oxidation are correct, then laminaritol will consist of a mixture of M-chains and sorbitol-terminated chains (S-chains). The laminaritol should therefore be resistant to lime-water, should be overoxidised to virtually the same extent as laminarin, and on periodate oxidation the rate of release of formaldehyde and formic acid should be increased.

The above conclusions have been verified experimentally. Lime-water at 60° had no appreciable action on laminaritol. On overoxidation with periodate, 0·55 mol. of formaldehyde was produced. On oxidation at pH 5, the formaldehyde production from laminaritol before and after lime-water treatment was unaltered. The maximum constant yield after only 6 hours' oxidation was 0·063 mol., equivalent to a $\overline{DP}$ of 24. Further, the amount of formic acid (*ca.* 0·13 mol.) released on total primary oxidation was, as expected, less than from laminarin, and the rate of production was increased.

Methylation of laminaritol gave a polysaccharide methyl ether with OMe 43·3%, and only 6% of this failed to be precipitated when light petroleum was added to a chloroform solution. The precipitated methylated laminaritol had a number-average molecular weight of 3800 ($\overline{DP}$ 19) from isothermal-distillation measurements.[17] This fractionation differed from that of methylated laminarin in that material of higher molecular weight ($\overline{DP}$ *ca.* 60) was not selectively precipitated.

The Molecular Structure of Laminarin.—From the evidence cited above we conclude that " laminarin " is heterogeneous with respect both to molecular weight and to chemical structure. The conditions used for its extraction (pH 3·4 and 55°) do not cause marked degradation (see p. 3239) and it seems probable that " native " laminarin is also heterogeneous. In agreement with Peat and his co-workers, we find that insoluble laminarin contains *ca.* 2% of mannitol, and that approximately one-half of the molecules are terminated by mannitol. Unrau and Smith[18] have concluded, independently, that 30% of M-chains were present in an unspecified sample of laminarin. The heterogeneous nature of the latter was also shown[18] by electrophoresis on glass-fibre paper. In addition, although the average $\overline{DP}$ of our laminarin is *ca.* 24, some of the molecules (78% *by weight*) have a $\overline{DP}$ of *ca.* 60 and are slightly branched with β-1 : 6-inter-chain linkages. The alternative suggestion[5] that the β-1 : 6-glucosidic linkages are located in non-terminal positions in a linear chain of β-1 : 3-linked glucose residues seems less likely since this structure, on methylation analysis, would yield a small quantity of 2 : 3 : 4-tri-*O*-methyl-glucose. This sugar has not been detected. Further, the number of triol groups in laminarin is the same by both methylation and periodate oxidation analysis, in agreement with a branched structure. In a linear-type structure, the number of triol groups detected by periodate would exceed that found from methylation.

The methylation analysis of laminarin is complicated, in part, by the presence of alkali-sensitive reducing groups and, in contrast to laminaritol, laminarin is partly degraded on methylation, the number-average molecular weight decreasing from *ca.* 4000 to *ca.* 1900. Similar observations have been made by Friedlaender, Cook, and Martin[19] who found partly methylated laminarin with OMe 2·7 and 6·9% had molecular weights (weight-average values from sedimentation-diffusion measurements) of 3700 and 2900 respectively. This degradation is presumably limited to G-chains, which are partly converted into methylated oligosaccharides with $\overline{DP}$ 2—3. (In our previous study,[3] these oligosaccharides would be separated from the methylated laminarin during the purification of the latter by dialysis.) However, the residual laminarin (78%) has an average chain length of 23, and a proportion of these molecules are slightly branched. It is of interest that many of these branched molecules are resistant to lime-water at 60° and are therefore terminated by mannitol residues.

[17] Broatch, Ph.D. Thesis, Edinburgh, 1956.
[18] Unrau and Smith, *Chem. and Ind.*, 1957, 330; see also Lewis and Smith, *J. Amer. Chem. Soc.*, 1957, **79**, 3929.
[19] Friedlaender, Cook, and Martin, *Biochim. Biophys. Acta*, 1954, **14**, 136.

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Experimental

Analytical Methods.—(a) *Paper chromatography.* The following solvents were used for the separation of glucose and mannitol: (*a*) phenol–water (72 : 28) with a silver nitrate identification spray; (*b*) ethyl methyl ketone–acetic acid–water, saturated with boric acid (9 : 1 : 1, v/v) [20] with a periodate–benzidine spray reagent.[21] The solvents used for the chromatography of oligosaccharides and methylated sugars have been described previously.[22]

(b) *Reducing power.* Somogyi's alkaline copper reagent [23] or Hagedorn and Jensen's potassium ferricyanide method [24] was used, with glucose and laminaribiose as standard sugars. Reducing power (R.P.) values are expressed as 100/No. of glucose residues per apparent reducing group (against laminaribiose standard).

(c) *Periodate oxidation.* The consumption of periodate and the production of formic acid were determined as described by Manners and Archibald.[11] Formaldehyde was estimated qualitatively with a chromotropic acid reagent [25] and quantitatively by the method of Hough, Powell, and Woods.[26]

Preparation and Properties of Insoluble Laminarin.—The laminarin was prepared by Dr. W. A. P. Black, Institute of Seaweed Research, Inveresk, as follows: Fresh *L. cloustoni* fronds, collected at Campbeltown (November, 1954), were minced (¼" mesh) and extracted for 1 hr. at 55—60° with ten parts (by wt.) of dilute hydrochloric acid solution (pH 3·4). After centrifugation, the weed residue was washed with water, and the combined extract and washings were set aside for 48 hr. The polysaccharide deposited was collected and washed with alcohol and ether. The yield represented 43% of the laminarin present in the fronds. The laminarin, purified by recrystallisation from hot water, had $[\alpha]_D$ −9° (*c* 1·5 in H_2O), +9° (*c* 2·7 in N-NaOH) [adsorbed alcohol,[27] 0·20; ash content, 0·45; glucose content (by cuprimetric titration), 94%; R.P. values, 2·5 (Somogyi), 5·9 (potassium ferricyanide)]. Hypoiodite oxidation indicated the presence of one reducing group per 47 glucose residues.

Stability of Laminarin at pH 3·4 *and* 55°.—Laminarin (1 g.) was heated at 55° with dilute hydrochloric acid solution (pH 3·4; 100 ml.). Samples were removed after 0, 30, and 60 min., cooled, and neutralised, and the reducing powers of 5 ml. portions were determined. No increase in reducing power was observed. The residual solution was cooled, neutralised, and evaporated to dryness. Oligosaccharides could not then be detected by paper chromatography.

Partial Acid Hydrolysis of Laminarin.—Laminarin (1 g.) was heated at 100° with 0·1N-oxalic acid (40 ml.) for 5·5 hr., cooled, and neutralised with calcium carbonate, and the filtrate, after concentration, was examined by paper chromatography. The hydrolysate contained glucose, laminaribiose, laminaritriose (by comparison of $R_{Glucose}$ values with those of authentic samples), R_G 0·45 (non-reducing), R_G 0·34, 0·24, and 0·16 (reducing). Laminaritetraose would have an R_G value of 0·24 under these conditions. In addition, smaller amounts of non-reducing oligosaccharides were present.

Complete Acid Hydrolysis of Laminarin.—Laminarin (1 g.) was hydrolysed with N-sulphuric acid (100 ml.) for 7·5 hr. at 100°, and the solution cooled, neutralised with barium carbonate, filtered, and evaporated to a syrup. The presence of glucose was shown by paper chromatography, with both aniline oxalate and silver nitrate sprays. Part of the syrup (0·1 g.) was incubated with glucose oxidase solution (5 ml.) at pH 7·0 for 40 hr. The residual sugar with R_G *ca.* 1 reacted with silver nitrate but not with aniline oxalate. Chromatography in phenol–water revealed a non-reducing carbohydrate with the R_G value of mannitol.

In later experiments, neutralised hydrolysates were chromatographed in the solvent containing boric acid. Authentic samples of mannitol and sorbitol had R_G 2·8 and 3·3 respectively. The hydrolysate contained non-reducing carbohydrates with R_G 2·8 and 1·6.

Methylation Analysis of Laminarin.—The polysaccharide (15 g.) was methylated four times at room temperature under nitrogen, with dimethyl sulphate and sodium hydroxide solution. The methylated polysaccharide was extracted with chloroform, and the extract washed with

[20] Rees and Reynolds, *Nature*, 1958, **181**, 767.
[21] Cifonelli and Smith, *Analyt. Chem.*, 1954, **26**, 1132.
[22] Chanda, Hirst, and Manners, *J.*, 1957, 1951.
[23] Somogyi, *J. Biol. Chem.*, 1952, **195**, 19.
[24] Hagedorn and Jensen, *Biochem. Z.*, 1923, **135**, 46.
[25] Mitchell and Percival, *J.*, 1954, 1423.
[26] Hough, Powell, and Woods, *J.*, 1956, 4799.
[27] Newman, *J. Pharmacol.*, 1936, **58**, 278.

water, dried, and concentrated (yield, 18·5 g., 98%) (Found: ash, 1·0; OMe, 44·0. Calc. for tri-*O*-methyl-laminarin: OMe, 45·6%).

Methylated laminarin (16·9 g.) was dissolved in chloroform (100 ml.), and light petroleum (b. p. 40—60°) added slowly until precipitation occurred. The material which was precipitated between 91 and 92·5% v/v light petroleum content was collected, washed, and dried (12·8 g., 78%; $[\alpha]_D$ −5·7° at *c* 1·1 in $CHCl_3$). No further polysaccharide was precipitated when the concentration of light petroleum was increased to 95%.

By isothermal distillation,[13] the original and the precipitated sample of methylated laminarin had molecular weights of 1900 and 12,000 respectively. An acid hydrolysate of the original methylated laminarin contained tetra-, tri-, and di-*O*-methylglucose (paper chromatography).

Precipitated methylated laminarin (5 g.) was hydrolysed with methanolic 4% hydrogen chloride (160 ml.) in a sealed tube at 100° for 6·5 hr. After neutralisation with silver carbonate, the filtrate was concentrated and hydrolysed with boiling aqueous N-hydrochloric acid (300 ml.) for 14 hr. The neutralised, concentrated hydrolysate was extracted with acetone and on evaporation 5·3 g. of methylated glucose derivatives were obtained.

The mixed sugars were chromatographed in butan-1-ol (15 ml.) on cellulose [28] (50 × 3 cm.), with light petroleum (b. p. 100—120°)–butan-1-ol saturated with water (7 : 3) as eluant. Three fractions were collected, comprising 4·85 g. of methylated sugars. Elution of the column with light petroleum–butan-1-ol (1 : 1) and then water yielded two further fractions (0·59 g.).

Fraction 1 (6 mg.) was not examined.

Fraction 2 (0·246 g.) contained 2 : 3 : 4 : 6-tetra-*O*-methylglucose (94%, by hypoiodite oxidation) and was homogeneous on paper chromatography; recrystallised from light petroleum (b. p. 40—60°) it had m. p. 85—86°; the derived anilide had m. p. 133—135°.

Fraction 3 (4·593 g.) was crystalline. It contained 2 : 4 : 6-tri-*O*-methylglucose (97%, by hypoiodite oxidation) {$[\alpha]_D$ +91° ⟶ +72° (*c* 0·92 in H_2O, after 24 hr.); m. p. and mixed m. p. 122—124°}. The corresponding anilide had m. p. and mixed m. p. 160—161°. The fraction was homogeneous on paper chromatography, even after prolonged development. The R_g values (tetra-*O*-methylglucose standard) of authentic 2 : 3 : 4- and 2 : 4 : 6-tri-*O*-methylglucose were 0·85 and 0·80 respectively.

Fraction 4, a syrup (0·491 g.), contained two methylglucoses [paper chromatography, R_g 0·59 (brown spot), R_g 0·62 (pink spot)], and gradually some crystals were formed. The fraction was dissolved in ethyl acetate and, on cooling, 4 : 6-di-*O*-methylglucose (R_g 0·59), m. p. 155—157°, mixed m. p. 154—156° (0·097 g.), was deposited. Evaporation of the ethyl acetate solution yielded a syrup (0·379 g.) which contained a sugar with R_g 0·62.

Since the mixed sugars contained 0·231 g. of tetra-*O*-methylglucose, the proportion of non-reducing end-groups is 4·4% or one per 23 glucose residues.

Degradation of Laminarin by Lime-water.—In extensive small-scale experiments laminarin was treated with lime-water for varying periods, at 25° or 60° in the presence or absence of oxygen. In a large-scale experiment laminarin (12 g.) was treated with saturated oxygen-free lime-water (1500 ml.) at 60° under nitrogen. Samples (5 ml.) were removed at intervals, and the consumption of lime-water determined by titration with 0·01N-hydrochloric acid. Reaction was complete after 23 hr. The mixture was neutralised with dilute nitric acid and concentrated to *ca.* 50 ml. The polysaccharide which was deposited on storage was collected by centrifugation, dissolved in water, and freeze-dried (yield, 5·5 g., 46% recovery). To the remaining solution, ethanol (80% v/v) was added and the resulting precipitate also dissolved in water and freeze-dried (yield, 4·5 g.). This material contained carbohydrates of low molecular weight which gave glucose on acid hydrolysis, saccharinic acid (48%), and non-lactonisable acid (19%) (estimated by the method of Bamford, Bamford, and Collins [29]), and had an ash content of 15%.

The lime-treated laminarin had $[\alpha]_D$ −7° (*c* 5·0 in H_2O), ash, 0·5%, and R.P. 0·3 (Somogyi), 1·7 (potassium ferricyanide); an acid hydrolysate contained mannitol (paper chromatography). Re-treatment with lime-water caused little further degradation, *ca.* 90% of polysaccharide being recovered.

On partial hydrolysis with oxalic acid, the hydrolysate of lime-treated laminarin contained the same series of sugars as that from the original laminarin. In a similar experiment with

[28] Hough, Jones, and Wadman, *J.*, 1949, 2511.
[29] Bamford, Bamford, and Collins, *Proc. Roy. Soc.*, 1950, *A*, **204**, 85.

another sample of lime-treated laminarin, the presence of a reducing sugar with the R_G value of gentiobiose was noted.

Methylation Analysis of Lime-treated Laminarin.—This polysaccharide (8·5 g.) was methylated eight times with dimethyl sulphate and sodium hydroxide, as described for laminarin (p. 3239). The methylated product (10·3 g., 96%) had ash 1·0, OMe, 44·1%. On addition of 94% v/v light petroleum (b. p. 40—60°) to a solution of methylated polysaccharide (9·2 g.) in chloroform (50 ml.), a precipitate (7·5 g., 88%) was obtained, having $[\alpha]_D$ −7·1° (*c* 1·3 in $CHCl_3$). The addition of further light petroleum (1 l.) to the supernatant solution did not give a precipitate.

The original and the precipitated sample of methylated lime-treated laminarin had molecular weights of 2500 and 13,600 respectively.[13]

The sample (4 g.) of high molecular weight was hydrolysed successively with methanolic 4% hydrogen chloride (130 ml.) and N-hydrochloric acid (300 ml.) as described previously, to give 4·4 g. of methylated glucose derivatives. Partition chromatography on a cellulose column gave five fractions:

Fraction 1, a syrup (0·294 g.) contained 2 : 3 : 4 : 6-tetra-*O*-methylglucose and methyl tri-*O*-methylglucoside. The major portion (0·240 g.) was re-hydrolysed with N-sulphuric acid (25 ml.) for 6 hr., neutralised, and concentrated. The resulting syrup was partitioned on a second cellulose column to give two fractions.

Fraction 1a (0·174 g.) contained crystalline 2 : 3 : 4 : 6-tetra-*O*-methylglucose, which after recrystallisation had m. p. 84—86°; the derived aniline derivative had m. p. and mixed m. p. 134—135°. Fraction 1b, a syrup (0·081 g.), contained 2 : 4 : 6-tri-*O*-methylglucose.

Fraction 2 (0·036 g.) contained tetra- (7 mg.) and 2 : 4 : 6-tri-*O*-methylglucose (29 mg.) (paper chromatography).

Fraction 3 (3·676 g.) crystallised. It was chromatographically homogeneous and contained 2 : 4 : 6-tri-*O*-methylglucose (94%, by hypoiodite oxidation). After recrystallisation from ether, the crystals had m. p. 124—126°, mixed m. p. 123—124°, $[\alpha]_D$ +94° ⟶ +73° (*c* 1·68 in H_2O, after 24 hr.). Its aniline derivative had m. p. and mixed m. p. 160—162°.

Fraction 4 (0·375 g.) was partly crystalline, and contained two sugars. One of these, after crystallisation from ethyl acetate, was identified as 4 : 6-di-*O*-methylglucose, m. p. and mixed m. p. 156—159°. The remaining sugar gave a pink colour with aniline oxalate.

Fraction 5 (0·074 g.) was a white amorphous solid which contained mono-*O*-methylglucose and a trace of glucose. It was not further investigated.

The percentage composition of the hydrolysate was: tetra- 5·2, tri- 84·4, 4 : 6-di- 1·5, unidentified di- 7·2, mono-*O*-methylglucose 1·8, indicating the presence of one non-reducing end-group per 20 glucose residues.

Preparation and Properties of Laminaritol.—Potassium borohydride (5 g.) was added to an aqueous solution of laminarin (10 g. in 500 ml.). After 48 hr., the mixture was neutralised (pH 7; acetic acid), and the polysaccharide precipitated with alcohol. The laminaritol was then dissolved in warm water, reprecipitated, redissolved, and finally freeze-dried. The product (9·6 g.) had glucose content 94%, ash content 1·2%, and R.P. 0·1 (Somogyi). A neutralised acid hydrolysate was examined by paper chromatography; comparison with authentic specimens showed the presence of glucose, mannitol, and sorbitol. Laminaritol (5·2 g.) was then treated with saturated lime-water (650 ml.) in an atmosphere of nitrogen at 60° for 23 hr. The solution was cooled, neutralised (pH 7; dilute nitric acid), and concentrated. Polysaccharide was slowly precipitated and after recovery by centrifugation was washed with water and freeze-dried (yield, 4·8 g.) (Found: ash content, 2·7%). Addition of alcohol to the lime-water solution gave a small precipitate (0·58 g.).

Methylation of Laminaritol.—Laminaritol (5 g.) was methylated six times with dimethyl sulphate and sodium hydroxide; the product was isolated by chloroform extraction (yield, 6·2 g.) (Found: OMe, 43·3%). It was dissolved in chloroform (35 ml.), and light petroleum (b. p. 40—60°) added until precipitation ceased (500 ml.). The recovery was 94%. The material (0·4 g.) which was soluble in light petroleum was recovered.

By isothermal distillation,[17] the insoluble material had a molecular weight of 3800.

Periodate Oxidation of Laminarin and Related Compounds.—(a) *Sodium metaperiodate at* 2°. Laminaribiose (150 mg.) and 3-*O*-methylglucose (50 mg.) were oxidised with 0·3M-sodium metaperiodate (10 ml.) in water (final vol. 200 ml.). Formaldehyde could not be detected during 3 days with the chromotropic acid reagent. The production of formaldehyde from

mannitol, under similar conditions, was complete within 1 hr. and the concentration of formaldehyde (1·8 mol.; theory 2·0) remained constant for 44 hr.

Laminarin (90·0 mg.) and laminaritol (74·9 mg.) were oxidised with 0·3M-sodium metaperiodate (2 ml.) in water (23 ml.). The liberation of formaldehyde from laminarin was as follows:

Time of oxidn. (hr.)	1	3	5	12	48
Formaldehyde prodn. (mol.)	0·022	0·023	0·023	0·023	0·025

This is equivalent to an initial release of 0·021 mol.

The results with laminaritol were:

Time of oxidn. (hr.)	22	44	88
Formaldehyde prodn. (mol.)	0·057	0·058	0·060

The production of formic acid from the control experiments was as follows:

Time (hr.)	2	5	24	72	4—6 days	8 days
Formic acid (mol.)						
Laminaribiose	0·50	0·77	1·18	1·51	1·72	2·08
3-*O*-Methylglucose	—	0·28	0·33	0·58	0·68	—

Under these conditions, 1 mol. of formic acid is produced from laminaribiose after *ca.* 14 hr.

The following results were obtained when laminarin (1 g.) was oxidised:

Time (hr.)	5	24	48	96	168
Periodate uptake (mol.)	0·16	0·19	0·19	0·20	0·21
Formic acid (mol.)	0·09	0·10	0·10	0·11	0·11

It follows that 0·10 mol. of acid is released during the initial primary oxidation.

The production of formic acid from laminaritol was 0·12 mol. after 22 and 44 hr., and 0·13 mol. after 66 and 94 hr., representing a total primary oxidation yield of 0·12 mol.

(b) *Sodium metaperiodate at room temperature.* Laminarin and laminaritol (*ca.* 50 mg.), dissolved in water, were treated with 0·3M-sodium metaperiodate (2 ml.) in a total volume of 25 ml. Samples (2 ml.) were analysed at intervals for formaldehyde:

Time of oxidn. (hr.)	6	23	48
Formaldehyde prodn. (mol.)			
Laminarin	0·032	0·040	0·042
Laminaritol	0·064	0·064	0·064

A duplicate analysis gave 0·040 and 0·061 mol. of formaldehyde, respectively, after 16 and 36 hours' oxidation. Lime-treated laminaritol gave 0·061 mol. under similar conditions.

(c) *Sodium metaperiodate at* pH 8 *and room temperature.* The polysaccharides (*ca.* 8 mg.; concentration determined by acid hydrolysis) were dissolved in water, phosphate buffer (0·1M, pH 8: 12·5 ml.), and 0·3M-sodium metaperiodate (2 ml.) in a total volume of 25 ml. The production of formaldehyde was constant after oxidation for 18 hr. and amounted to 0·52 mol. from laminarin, and 0·55 mol. from laminaritol. Under these conditions, the residual polysaccharide was stable, even after oxidation for 9 days. In a further experiment, lime-treated laminaritol gave 0·57 mol. of formaldehyde.

(d) *Potassium metaperiodate at room temperature.* Laminaribiose (35·5 mg.) and mannitol (17·8 mg.) were dissolved in 3% potassium chloride solution (25 ml.), and 0·25M-sodium metaperiodate (25 ml.) was added. The production of formic acid was determined at intervals, and a reagent control was also analysed. Liberation of acid from mannitol ceased after 4 hr. and corresponded to 3·7 mol. Laminaribiose gave the following results:

Time (hr.)	2	4	6	24	48	96	144	168
Formic acid (mol.)	0·38	0·65	0·96	1·38	1·81	2·60	3·08	3·13

Under these conditions (pH 5; cf. Part I), the initial and the total primary oxidation require *ca.* 6 and 130 hr. respectively, and over-oxidation after this time is slight.

Laminarin (235·9 mg.) was oxidised as above:

Time (hr.)	3	6	18	42	168	240
Formic acid (mol.)	0·088	0·096	0·114	0·126	0·156	0·163

The initial and total primary oxidations therefore yield *ca.* 0·10 and *ca.* 0·15 mol. of formic acid, respectively.

Laminaritol (244·9 mg.) was similarly oxidised:

Time (hr.)	2	13	20	38	144	240
Formic acid (mol.)	0·081	0·113	0·122	0·131	0·153	0·168

The total primary oxidation corresponded to *ca.* 0·13 mol., and the rate of production of formic acid was significantly greater than from laminarin. It is apparent that slow overoxidation of laminarin and laminaritol occurs after potassium metaperiodate oxidation for approximately 150 and 100 hr. respectively.

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664. *The Preparation of Some New Substituted Naphthylamines and Naphthidines.*

By R. BELCHER, S. J. LYLE, and W. I. STEPHEN.

The preparation of some new 1-substituted 2-*n*- and 2-*iso*-propyl naphthalenes is described.

The Fries and Lohmann oxidation of 2-methyl-1-naphthylamine to 3 : 3′-dimethylnaphthidine is applied to the oxidation of a number of 2-substituted 1-naphthylamines and is shown to be a general reaction for the preparation of 3 : 3′-disubstituted naphthidines. A mechanism is suggested for the reaction and some limitations are noted. A few naphthidines not obtainable by this reaction are prepared by other methods.

NAPHTHIDINE (I; R = H) is usually obtained by reducing 1 : 1′-azonaphthalene with stannous chloride in hydrochloric acid [1] or by oxidation of 1-naphthylamine with ferric oxide in 88% sulphuric acid.[2] 3 : 3′-Dimethylnaphthidine (I; R = Me) has been prepared by oxidation of 2-methyl-1-naphthylamine with ferric oxide in 66% sulphuric acid.[3] Both naphthidines prepared by these methods are heavily contaminated with, and difficult to free from, metal salts.

In view of the disadvantages associated with the above methods, Fries and Lohmann's method [4] has been investigated and shown to be general for the preparation of 3 : 3′-disubstituted naphthidines (I) from 2-substituted 1-naphthylamines. Fries and Lohmann found that treatment of 2-methyl-1-naphthylamine sulphate in hot acetic acid with a few drops of perhydrol resulted in a vigorous reaction, with deposition of a salt of the naphthidine (II; R = Me). They observed that 2-methyl-1-naphthylamine did not itself give the naphthidine and that 1-naphthylamine did not give naphthidine. It has now been found that sulphates of 2-ethyl-, 2-propyl-, 2-*iso*propyl-, 2-methoxy-, and 2-phenyl-1-naphthylamine react under the conditions described by Fries and Lohmann to give the corresponding naphthidine. With 2-chloro-, 2-bromo-, 2-hydroxy-, 2-nitro-, or 2-sulpho-1-naphthylamine, the corresponding naphthidine was not formed.

1-Naphthylamine, unless substituted in the 2-position, shows little inclination towards reaction. Substitution of benzoyl peroxide for perhydrol in the preparation of 3 : 3′-dimethylnaphthidine is not so efficient in the Fries and Lohmann reaction. Addition of water (5—10%) or sulphuric acid (1—2%) does not impair the yield of the naphthidine provided that the solubility of the naphthylamine salt is not affected. Reaction does not

[1] Cohen and Oesper, *J. Ind. Eng. Chem.* (Anal. Ed.), 1936, **8**, 306.
[2] Sah and Yuin, *Rec. Trav. chim.*, 1939, **58**, 751.
[3] Fierz-David, Blangey, and Dübendorfer, *Helv. Chim. Acta*, 1946, **29**, 1661.
[4] Fries and Lohmann, *Ber.*, 1921, **54**, 2912.

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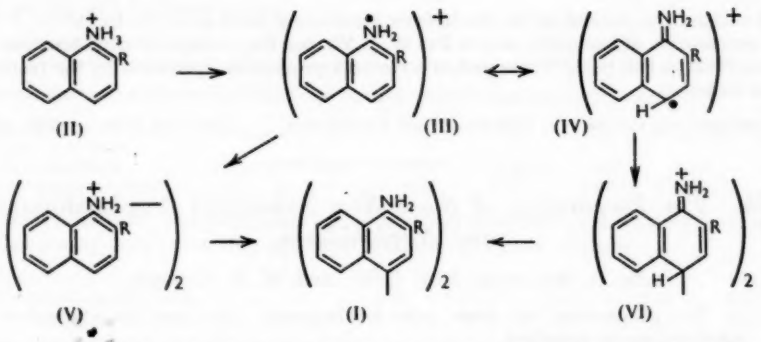
take place with *N*-acetyl derivatives of reactive naphthylamines even on prolonged boiling in acetic acid with perhydrol. It is also probably significant that 2 : 2′-dimethyl-1 : 1′-azonaphthalene cannot be prepared by Cohen and Oesper's method [1] and that Fierz-David and Mannhart [5] were unable to prepare this compound by reducing 2-methyl-1-nitronaphthalene with zinc dust in alkaline solution.

Possible Reaction Mechanisms.—The course of this reaction in some ways appears to be similar to that of the oxidation of diphenylamine to *NN*-diphenylbenzidine. In the



absence of acids, diphenylamine is oxidised to tetraphenylhydrazine [6] which is known to dissociate into the free radical $Ph_2N\cdot$, and which also undergoes the benzidine rearrangement. However, under conditions in which the hydrazine is dissociated, the benzidine change does not take place.[7] Oxidation with dichromate of diphenylamine in acetic acid containing a little sulphuric acid gives *NN*′-diphenylbenzidine in 20% yield, but *N*-acetylation prevents this reaction. Oxidation in 25% sulphuric acid to diphenylbenzidine-violet gives diphenylbenzidine in 60% yield by reduction.[8] From this evidence it would seem that oxidation of the naphthylamine salt (II) could give rise to the radical (III) by a mechanism similar to that suggested by Saunders and Watson [9] for the oxidation of *NNN*′*N*′-tetramethylbenzidine. Since the benzidine rearrangement is an intramolecular reaction [10] having specific hydrogen-ion catalysis with second-order dependence on hydrogen ions,[11] dimerisation of (III) could give rise directly to the protonated activation complex (V), which rearranges with loss of two hydrogen ions to (VII). However, by analogy with the oxidation of naphthols to dinaphthyldiols in alkaline solution [12] and oxidation of tertiary amines such as dimethylaniline, the radical (III) in the mesomeric form (IV) could dimerise to the intermediate (VI), which rearranges to the naphthidine (I). As yet, there is not sufficient evidence to distinguish between these two mechanisms.

Oxidation of 1-*Naphthylamines with Other Oxidants.*—Naphthidines, like benzidines, give intense colours on oxidation in neutral or acid solution. 1-Naphthylamines will, on oxidation in strong acid solution, give the same colour reactions as the corresponding naphthidines, suggesting that the naphthylamine is first oxidised to the naphthidine (I). 1-Aminonaphthalene-2-sulphonic acid can only be oxidised to the colour characteristic of the naphthidine by powerful oxidants (*e.g.*, Ce^{IV}). This would suggest that hydrogen peroxide is too weak to convert this naphthylamine into the naphthidine in the Fries and Lohmann reaction. 3 : 3′-Dinitronaphthidine (see below) cannot be oxidised with any

[5] Fierz-David and Mannhart, *Helv. Chim. Acta*, 1937, **20**, 1031.
[6] Chattaway and Ingle, *J.*, 1895, **67**, 1090.
[7] Wieland and Gambarjan, *Ber.*, 1906, **39**, 1503.
[8] Marqueyrol and Muraour, *Bull. Soc. chim.*, 1914, **15**, 186.
[9] Saunders and Watson, *Biochem. J.*, 1950, **46**, 629.
[10] Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, pp. 631—637.
[11] Hammond and Shine, *J. Amer. Chem. Soc.*, 1950, **72**, 220.
[12] Waters in H. Gilman (Ed.), "Organic Chemistry," Wiley, 1953, Vol. IV, p. 1216.

oxidant, so that it is hardly surprising that the Fries and Lohmann reaction fails with 2-nitro-1-naphthylamine.

Preparation of Naphthylamines.—The 2-substituted 1-naphthylamines are generally prepared by nitration of 2-substituted naphthalenes, followed by reduction to the amines. 2-Ethyl-1-naphthylamine was prepared by this route following the method described by Levy.[13] 2-Ethylnaphthalene is more conveniently prepared by reducing methyl 2-naphthyl-ketone by Huang-Minlon's method [14] rather than by Sah's use [15] of the Clemmensen procedure. Similarly, 2-*n*-propyl-1-naphthylamine was synthesised from ethyl 2-naphthyl ketone, made by Buu-Hoï and Caigniant's method. Oxidation of the product in strong mineral acid gave the purple-red colour associated with the lower homologues and the corresponding naphthidines, which supported the structure assigned; further evidence was provided by hydrolysis of the *N*-acetyl derivative to the known 2-*n*-propyl-1-naphthol.[17] 2-*iso*Propyl-1-naphthylamine was prepared similarly. Two independent syntheses of 2-*iso*propylnaphthalene have been examined, but neither gave very satisfactory yields, in agreement with the findings of Fieser and Chang.[18] The more convenient Friedel–Crafts synthesis described by Haworth *et al.*[19] is preferred to Bergmann and Weizmann's method [20] which probably gives a purer product, but polymerisation of the 2-2′-naphthyl-propene during the " dehydration " of 1-methyl-1-2′-naphthylethanol is difficult to prevent. The required mononitro-compound is isolated from the lower-boiling fractions of the nitration products of 2-*iso*propylnaphthalene. 2-*iso*Propyl-1-naphthylamine gives on oxidation in strong acid solution the characteristic purple-red colour associated with the other 2-alkyl-1-naphthylamines described. 2-Phenyl-1-naphthylamine was prepared according to Hey and Lawton.[21]

The naphthylamines described above are dissolved in ether and their sulphates are precipitated by addition of a solution of sulphuric acid in ether. These amine salts are converted into the corresponding naphthidines in 25—40% yields by the Fries and Lohmann reaction.

Other Naphthidines.—Hodgson and Habeshaw [22] reported the synthesis of 3 : 3′-dinitronaphthidine by nitrating 4 : 4′-diacetamido-1 : 1′-dinaphthyl. We have been unable to hydrolyse the nitrated diacetamido-compound either under the conditions described by these authors or by extending the time of hydrolysis. Deacetylation proceeds smoothly, however, in equal volumes of 10N-hydrochloric acid and ethanol. Reduction of the dinitronaphthidine to the diaminonaphthidine is readily effected with sodium dithionite. The diaminonaphthidine is very unstable to light and oxidising agents but it condenses readily with benzil (2 mols.), thus proving the compound to be 3 : 3′-diaminonaphthidine. Naphthidine-3 : 3′-disulphonic acid is prepared by reducing 1 : 1′-azonaphthalene-2 : 2′-disulphonic acid, synthesised by Cumming and Muir's method,[23] with stannous chloride in hydrochloric acid solution. The naphthidinedisulphonic acid differs from 1-naphthylamine-2-sulphonic acid used in its preparation in having a higher decomposition point and giving an *S*-benzylthiuronium derivative having a considerably lower m. p.

Experimental

M. p.s above 100° have been corrected.

Fries and Lohmann Reaction: General Procedure.—The naphthylamine salt (5 g.) is dissolved in sufficient warm acetic acid to prevent crystallisation when the mixture is cooled to 25—30°. The mixture is heated to boiling point, the source of heat removed, and hydrogen peroxide

[13] Levy, *Compt. rend.*, 1932, **195**, 801.
[14] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.
[15] Sah, *Rec. Trav. chim.*, 1940, **59**, 1021.
[16] Buu-Hoï and Caigniant, *Bull. Soc. chim.*, 1945, **12**, 307.
[17] Stroughton, *J. Amer. Chem. Soc.*, 1935, **57**, 202.
[18] Fieser and Chang, *ibid.*, 1942, **64**, 2050.
[19] Haworth, Letsky, and Mavin, *J.*, 1932, 1784.
[20] Bergmann and Weizmann, *J. Org. Chem.*, 1944, **9**, 352.
[21] Hey and Lawton, *J.*, 1940, 374.
[22] Hodgson and Habeshaw, *J.*, 1947, 1573.
[23] Cumming and Muir, *J. Royal Tech. Coll. Glasgow*, 1937, **4**, 63.

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(5—10 drops, 30% w/v) added immediately. When the mixture is cooled the crude naphthidine salt separates, is filtered off, and washed with acetic acid (5 ml.), the wash solution being collected with the main filtrate. The liquid is then treated with hydrogen peroxide by the same cycle of operations, the precipitate is collected and treatment of the filtrate continued until precipitation ceases. The precipitates are combined and washed well with water.

2-*Ethylnaphthalene*.—Methyl 2-naphthyl ketone (51 g.), 80% (w/w) hydrazine hydrate (30 g.), sodium hydroxide (36 g.), and diethylene glycol (300 c.c.) were heated under reflux for 1 hr. Water and excess of hydrazine (*ca.* 30 c.c.) were removed by distillation until the temperature rose to 190—200° and the mixture was then refluxed for 4 hr. more, then cooled and diluted with water to 750 c.c. The distillate and the refluxed mixture were combined and extracted with ether (150-c.c. portions) until the extract no longer showed a blue fluorescence. The extract was dried, the ether removed, and the residue distilled in the presence of sodium. The fraction (43 g.), b. p. 127·5—128·5°/18 mm., was collected. It gave a picrate, m. p. 77°.

3 : 3′-*Diethylnaphthidine*.—The crude naphthidine salt, obtained by the Fries and Lohmann reaction, was stirred for 15 min. in 10% sodium hydroxide (100 c.c.). The base was filtered off and washed free from alkali. It was dissolved in ethanol (25 c.c.), treated with activated carbon, and filtered hot. The filtrate was heated to boiling and water was added slowly until a definite turbidity persisted. On cooling, 3 : 3′-diethylnaphthidine monohydrate (1 g.) separated in red-violet needles, m. p. 110—116°. A pure, colourless sample was obtained by dehydration under reduced pressure at 70—80° and recrystallisation from ligroin. The pure anhydrous *base* melted at 103° (sealed capillary) (Found: C, 84·7; H, 7·3; N, 8·2. $C_{24}H_{24}N_2$ requires C, 84·6; H, 7·1; N, 8·2%).

2-n-*Propylnaphthalene*.—The method was that used in the preparation of the lower homologue, starting with ethyl 2-naphthyl ketone (55·2 g.). The fraction (42 g.), b. p. 133·5—135·5°/12 mm., was collected. It gave a picrate, m. p. 90°.

1-*Nitro*-2-n-*propylnaphthalene*.—2-*n*-Propylnaphthalene (85·1 g.) in acetic acid (125 c.c.) was treated with nitric acid (40 g., *d* 1·5) dropwise, the mixture being stirred and kept below 10°. It was allowed to reach room temperature and remain there for 2 hr. before being warmed gradually (3 hr.) to 80°, with rapid stirring throughout. The mixture was poured into water (1 l.) and extracted with ether. The extract was washed with 10% sodium carbonate solution, then water, and finally dried. The products (106 g.), after removal of the ether, were fractionated (Vigreux column, 25 cm. long). The fractions, b. p. 178—182°/18 mm. and 183—185°/18 mm., yielded a solid on cooling (−15°) and seeding, if necessary. (Pure crystals of 1-*nitro*-2-n-*propylnaphthalene* were first obtained by chromatographic separation of the nitrated oil on alumina.) A third fraction, b. p. 186—190°/18 mm., gave the solid, heavily contaminated with an oil. Two recrystallisations of the solid from ligroin (b. p. 40—60°) gave the pure compound (19 g.), m. p. 31° (Found: C, 72·3; H, 6·1; N, 6·3. $C_{13}H_{13}O_2N$ requires C, 71·5; H, 6·1; N, 6·5%).

2-n-*Propyl*-1-*naphthylamine*.—1-Nitro-2-*n*-propylnaphthalene (18·5 g.) in boiling 50% acetic acid (225 ml.) was treated gradually with iron powder (18·5 g.) and refluxed for 4 hr. 10N-Hydrochloric acid (100 c.c.) was added to the cooled reaction mixture which was then left overnight at 0°. The amine hydrochloride was filtered off and distilled in steam, first from 4N-hydrochloric acid (300 c.c.) to remove unchanged nitro-compound and then from alkaline solution. The amine was extracted into ether, and converted into 2-n-*propyl*-1-*naphthylammonium hydrogen sulphate* with 10% sulphuric acid in ether (Found: C, 55·0; H, 5·9; N, 5·1; S, 11·4. $C_{13}H_{17}O_4NS$ requires C, 55·1; H, 6·1; N, 5·0; S, 11·3%). The free base melted at 8—9°. The *acetyl derivative*, from pyridine with acetyl chloride, had m. p. 152° (Found: C, 79·2; H, 7·4; N, 6·3. $C_{15}H_{17}ON$ requires C, 79·3; H, 7·5; N, 6·2%).

2-n-*Propyl*-1-*naphthol*.—Two thick-walled hard-glass tubes were each charged with *N*-acetyl-2-*n*-propyl-1-naphthylamine (1·25 g.) and sulphuric acid (2·5 g., in 40 c.c. of water); the tubes were sealed and heated at 210° for 7 hr. The brown oil was extracted into chloroform and the chloroform solution was repeatedly extracted with 2N-sodium hydroxide. The combined alkaline extracts were acidified and extracted with ether. The ether solution was washed free from acid and dried, and the ether removed. The residue was distilled under reduced pressure and the solid brown distillate was recrystallised twice from ligroin; it formed needles (0·5 g.), m. p. and mixed m. p. 49—50°.

The *toluene*-p-*sulphonate* had m. p. and mixed m. p. 86° (Found: C, 70·7; H, 5·9; S, 9·4. $C_{20}H_{20}O_3S$ requires C, 70·6; H, 5·9; S, 9·4%).

3 : 3′-*Di*-n-*propylnaphthidine*.—The crude free base (1·1 g.) was obtained by stirring a suspension of the naphthidine salt, prepared by the Fries and Lohmann reaction, in 10% sodium hydroxide solution (100 c.c.) at 40—50° for 30 min. The base could not be purified by recrystallisation, but the NN′-*diacetyl derivative* (1 g.), m. p. 348°, was prepared from the crude base (1·1 g.) and acetyl chloride in pyridine, and this was readily purified by 3 recrystallisations from acetic acid (charcoal) (Found: C, 79·5; H, 7·2; N, 6·4. $C_{30}H_{32}O_2N_2$ requires C, 79·6; H, 7·1; N, 6·2%).

The diacetyl derivative (1·5 g.) was hydrolysed by a refluxing mixture of 10N-hydrochloric acid (250 c.c.) and ethanol (250 c.c.) for 60 hr. The *naphthidine dihydrochloride* (1·4 g.) was filtered off from the cooled solution (Found: C, 71·2; H, 6·9; Cl, 16·1. $C_{26}H_{30}N_2Cl_2$ requires C, 70·8; H, 6·9; Cl, 16·1%). The *base*, liberated by grinding the dihydrochloride with aqueous ammonia, was recrystallised from ligroin, forming white silky needles, m. p. 100° (Found: C, 84·7; H, 7·6; N, 7·8. $C_{26}H_{28}N_2$ requires C, 84·8; H, 7·7; N, 7·6%).

1-*Nitro*-2-iso*propylnaphthalene*.—By the method used for the isolation of the 2-*n*-propyl isomer, 2-*iso*propylnaphthalene (85 g.) yielded 1-*nitro*-2-iso*propylnaphthalene* (6 g.), m. p. 52° (Found: C, 72·2; H, 6·0; N, 6·6%).

2-iso*Propyl*-1-*naphthylamine*.—(*a*) 1-Nitro-2-*iso*propylnaphthalene (7·5 g.) in 50% acetic acid (95 c.c.) was reduced to the amine with iron powder (7·5 g.) in the same way as the *n*-propyl isomer. Steam distillation gave a solid which recrystallised in tablets, m. p. 70°, from ligroin (90—95% yield) (Found: C, 84·0; H, 8·0; N, 7·7%). *Acetyl derivative*, m. p. 187° (Found: C, 78·9; H, 7·3; N, 6·1%).

(*b*) After nitration of 2-*iso*propylnaphthalene (0·5 mol.), the fraction, b. p. 182—190°/18 mm. (50 g.), was treated in 50% acetic acid (600 c.c.) with iron powder (50 g.) in the same way as the pure nitro-compound. Steam-distillation from acid gave an oil which solidified when seeded with the pure amine and yielded 2-*iso*propyl-1-naphthylamine (10 g.), m. p. 70°, after 3 recrystallisations from ligroin.

3 : 3′-*Diiso*propylnaphthidine.—The naphthylamine salt (5 g.) readily yielded this naphthidine by the Fries and Lohmann reaction. The base was obtained by suspending the naphthidine salt in ethanol (100 c.c.), and adding 20% sodium hydroxide (20 c.c.). The mixture was boiled for 10 min., cooled, and filtered, and the solid (0·7 g.) was washed free from alkali. It recrystallised from ligroin in small cubes, m. p. 260° (Found: C, 84·6; H, 7·6; N, 7·4%).

3 : 3′-*Dimethoxynaphthidine*.—The crude naphthidine salt was obtained by the Fries and Lohmann reaction. The free base, obtained from a suspension of the salt in 10% sodium hydroxide, was first partially purified by dissolving it in ethanol, treating the solution once or twice with activated carbon, and precipitating the base by making the boiling filtrate turbid with water and cooling; the yield was 0·3—0·5 g. Recrystallisation from ligroin (charcoal) gave the pure *naphthidine* in pale yellow flakes, m. p. 218° (Found: C, 76·8; H, 5·6; N, 8·2. $C_{22}H_{20}O_2N_2$ requires C, 76·7; H, 5·8; N, 8·1%).

3 : 3′-*Diphenylnaphthidine*.—2-Phenyl-1-naphthylamine sulphate (5 g.) dissolved in acetic acid (50 c.c.) gave the corresponding naphthidine salt by the Fries and Lohmann reaction. The latter salt was very difficultly soluble in water and the free base was best obtained by warming the salt in ethanol (100 c.c.) and aqueous 20% sodium hydroxide (20 c.c.) until dissolution was complete. The solution was then filtered, and the amine precipitated with water. The precipitate was washed free from alkali on the filter and dissolved in ethanol (charcoal). After filtration, the filtrate was made turbid at the b. p. with water; the purified *naphthidine* (1·5 g.) separated on cooling as a greyish-purple solid; after recrystallisation from ligroin it had m. p. 219° (Found: C, 87·9; H, 5·4; N, 6·3. $C_{32}H_{24}N_2$ requires C, 88·0; H, 5·5; N, 6·4%).

3 : 3′-*Dinitronaphthidine*.—Finely powdered 4 : 4′-diacetamido-3 : 3′-dinitro-1 : 1′-dinaphthyl (2 g.) was refluxed with ethanol (75 c.c.) and 10N-hydrochloric acid (75 c.c.) for 48 hr. The initially pale yellow suspension gradually assumed a deep orange colour. The mixture was poured into water (500 c.c.), and the precipitate was filtered off, washed well with water, and dried. It was dissolved in the minimum quantity of boiling pyridine, and the hot solution filtered and made permanently turbid at the b. p. with water. The *naphthidine* (1·6 g.) formed bronze leaflets having a metallic lustre, m. p. 360° (Found: C, 64·0; H, 3·8; N, 14·8. $C_{20}H_{14}O_4N_4$ requires C, 64·2; H, 3·8; N, 15·0%).

3 : 3′-*Diaminonaphthidine*.—Sodium dithionite (4 g.) was added to 3 : 3′-dinitronaphthidine (0·5 g.) in ethanol (100 c.c.) and water (25 c.c.); the mixture was refluxed for 1 hr., solvent

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(75 ml.) was then distilled off, and the residual suspension poured into water (300 c.c.). The white solid (0·4 g.) was washed with water and dried. The amine formed a faintly yellow, fluffy solid (from ethanol) which had no definite m. p. and rapidly darkened in air and light.

The *diquinoxaline derivative* was prepared by dissolving 3 : 3′-diaminonaphthidine (0·2 g.) in the minimum amount of boiling ethanol and adding a solution of benzil (0·27 g.) in ethanol. The mixture was refluxed for 30 min., cooled, and filtered, and the solid benzil condensate was washed with aqueous ethanol. It recrystallised from pyridine–ethanol as pale yellow flakes, m. p. 362—363° (Found: C, 87·1; H, 4·7; N, 8·6. $C_{48}H_{30}N_4$ requires C, 87·0; H, 4·6; N, 8·4%). It dissolved in concentrated sulphuric acid to give an intense red colour.

Naphthidine-3 : 3′-disulphonic Acid.—1 : 1′-Azonaphthalene-2 : 2′-disulphonic acid (2·5 g.) was dissolved in 5N-hydrochloric acid (150 c.c.) and treated dropwise with a 20% solution of stannous chloride in 10N-hydrochloric acid, until the hot solution became colourless (*ca.* 5 min.). A white precipitate separated and boiling was continued for 30 min. The mixture was cooled, and the solid filtered off. It was dissolved in aqueous ammonia and the solution boiled for 5 min. and filtered. The filtrate was acidified and the precipitate recrystallised from boiling water forming white lustrous leaflets (*ca.* 2 g.). The naphthidine was very hygroscopic and gradually decomposed above 300° (Found: C, 53·8; H, 3·7; N, 6·3; S, 14·4. $C_{20}H_{16}O_6N_2S_2$ requires C, 54·0; H, 3·6; N, 6·3; S, 14·4%).

The S-*benzylthiuronium derivatives* were prepared as follows: (*a*) The 1-naphthylamine-2-sulphonic acid derivative was precipitated from neutral solution with *S*-benzylthiuronium chloride; it formed large white leaflets, m. p. 184°, from aqueous ethanol (Found: C, 55·5; H, 4·8. $C_{18}H_{19}O_3N_3S_2$ requires C, 55·5; H, 4·9%). (*b*) The naphthidine-3 : 3′-disulphonic acid derivative, prepared similarly, was a pale tan powder, m. p. 144°, from aqueous ethanol (Found: C, 55·2; H, 4·8. $C_{36}H_{36}O_6N_6S_4$ requires C, 55·6; H, 4·7%).

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CHEMISTRY DEPARTMENT,
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665. *Tracer Studies in Ester Hydrolysis. Part VI.* The Hydrolysis of Methyl Trifluoroacetate.*

By C. A. BUNTON and T. HADWICK.

The acyl–oxygen bond of methyl trifluoroacetate is broken during hydrolysis in acid, alkaline, or initially neutral solution. Substitution of fluorine in the acyl group of the ester increases the rate of hydrolysis in alkaline or initially neutral aqueous dioxan, but relatively decreases the rate in acid, and the extent of acid-catalysis is small compared with that for unfluorinated esters. Added salts decrease the rate of the neutral hydrolysis.

The dissociation constant of trifluoroacetic acid in aqueous dioxan has been estimated colorimetrically.

SUBSTITUTION of electron-attracting atoms or groups into the acyl group of a carboxylic ester is known to increase the rate of nucleophilic attack on the acyl-carbon atom.[1] It will also make it easier for the ester to ionise, giving carbonium and carboxylate ions, or for the nucleophilic reagent to displace the carboxylate ion from the alkyl group, and it has been suggested that the extent of alkyl–oxygen bond fission in the hydrolysis of an ester of a carboxylic or other acid can give a measure of the strength of the acid.[2] Such a method could be misleading if the mechanism and kinetic form of the hydrolysis were not known.

* Part V, *J.*, 1957, 3043.

[1] Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686.
[2] Anbar, Dostrovsky, Klein, and Samuel, *J.*, 1954, 3603.

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Trifluoroacetic acid is very much stronger than other carboxylic acids, because of the powerful electron-attraction by the three fluorine atoms, and it is largely dissociated in dilute solution in water, but in concentrated aqueous solution it is considerably weaker than the strong mineral acids.[3]

Esters of trifluoroacetic acid have been known for some time,[4] but the first work to give information on the mechanism of their formation and hydrolysis is that of Traynham.[5] The esters of (−)-octan-2-ol with trifluoroacetic and perfluorobutyric acid were prepared by direct esterification, or by reaction between the alcohol and the acid chlorides. The optically active esters were then hydrolysed with alkali, to regenerate alcohol with no loss of activity. This suggests that both acid esterification and alkaline hydrolysis break the acyl–oxygen bond. It has also been shown spectroscopically that a stable entity is formed by reaction between ethyl trifluoroacetate and ethoxide ions, presumably by nucleophilic addition to the acyl-carbon atom.[6]

The rates of hydrolysis of esters of fluoro-carboxylic acids have been measured by several investigators. The rates of hydrolysis of ethyl esters in initially neutral aqueous acetone increase with increasing fluorination, and autocatalysis was observed for some reactions.[7] It was also found that the rate of hydrolysis of ethyl trifluoroacetate was doubled by the addition of 0·05M-hydrochloric acid. More recently the hydrolyses (in initially neutral aqueous acetone) of *n*-alkyl trifluoroacetates have been followed conductimetrically.[8] The rate decreased, with increasing chain length, to a limiting value; similar results have been found for the hydrolysis of *n*-alkyl benzoates.[9] It was assumed that the conductivity varied linearly with concentration of trifluoroacetic acid. This is probably not correct, because the acid is only partially dissociated in this aqueous-acetone solvent.[10]

These kinetic and stereochemical experiments are consistent with acyl–oxygen fission for both esterification and hydrolysis, but they do not exclude the possibility that alkyl–oxygen bond fission might occur in some cases.

Results

Bond Fission.—Methanol was isolated, by fractional distillation, from hydrolyses with the water enriched in ^{18}O. Two sets of conditions were used: heterogeneous hydrolysis in water, and homogeneous hydrolysis in dioxan–water 60 : 40 (v/v). The results are given in Table 1. In all cases the acyl–oxygen bond was broken.

Table 1. *Position of bond fission.*

	Homogeneous		Heterogeneous		
Reagent	—	$HClO_4$ (0·45M)	—	$HClO_4$ (0·891M)	NaOH (0·49M)
N_{MeOH} (atom % excess)	0·00	0·004	0·005	0·004	0·013

N_{H_2O} = 0·59 atom % excess; for the acid experiments this was diluted to a small extent by the water contained in 72% perchloric acid.

Kinetics.—The rates of hydrolysis in initially neutral aqueous dioxan were followed by three independent methods. The trifluoroacetic acid was estimated conductimetrically, or iodometrically; these methods gave consistent results, but dilatometry gave rate constants which were too high (see p. 3254). The conductimetric method was sufficiently sensitive to detect autocatalysis by trifluoroacetic acid. Results are in Table 2.

[3] Long and Paul, *Chem. Rev.*, 1957, **57**, 1.
[4] Swarts, *Bull. Acad. Roy. Belg., Classe Sci.*, 1922, **8**, 343; Bourne, Tatlow, and Tatlow, *J.*, 1950, 1367.
[5] Traynham, *J. Amer. Chem. Soc.*, 1952, **74**, 4277.
[6] Bender, *ibid.*, 1953, **75**, 5986.
[7] Gorrin, Pierce, and McBee, *ibid.*, p. 5622.
[8] Moffat and Hunt, *ibid.*, 1957, **79**, 54.
[9] Tommila, *Ann. Acad. Sci. Fennicae*, 1942, *A*, **59**, No. 3.
[10] Pierce and Gorrin, *J. Amer. Chem. Soc.*, 1953, **75**, 1749.

TABLE 2. *Rates of hydrolysis in aqueous dioxan. Initially neutral solution. Titrimetric and dilatometric methods.*

Dioxan–water 70 : 30 (v/v).

Temp.	0°	25·0°	44·6°
10^5k_1 (sec.$^{-1}$)	1·80	10·0	24·0

Dioxan–water, 60 : 40 (v/v).

Temp.	0°	25·0°	34·8°	44·6°
10^5k_1 (sec.$^{-1}$)	5·47, 4·62 [a]	23·6, 25·0, 33·7 [D]	39·8	74·4

[a] [$LiClO_4$] 0·567M.

Dioxan–water, 40 : 60 (v/v). Temp. 0°.

Reagent	0·482M-$LiClO_4$	0·567M-Et_4NBr	—
10^5k_1 (sec.$^{-1}$)	21·8	20·9	33·2 [D]

[D] Values so marked were obtained dilatometrically, and are included to show the error of the method for neutral hydrolyses.

Conductimetric method, showing the autocatalysis.

Dioxan–water, 60 : 40 (v/v). Temp. 0°, unless otherwise specified.

[CF_3·CO_2Me] (initial) (M)	0·058	0·058 *	0·060 †	0·036 ‡
10^5k_1 (sec.$^{-1}$) (initial)	5·42	7·17	24·6	25·6
,, (final)	7·11	—	30·4	30·7

* CF_3·CO_2H added initially = 0·058M. † Temp. 25·0°. ‡ Dioxan–water, 40 : 60 (v/v).

The Arrhenius equations are (from titrimetric and conductimetric results):

Dioxan–water, 70 : 30 (v/v); $k_1 = 10^{8\cdot9} \exp(-10{,}500/RT)$ (sec.$^{-1}$).
,, 60 : 40 (v/v); $k_1 = 10^{8\cdot4} \exp(-10{,}200/RT)$ (sec.$^{-1}$).

Acid solutions. Temp. 0°, and dilatometric results unless otherwise specified.

Dioxan–water, 70 : 30 (v/v).

[$HClO_4$] (M)	0·27	0·50	0·92	0·98	1·47
10^5k_1 (sec.$^{-1}$)	8·30	18·2	22·7	24·0	20·4

Dioxan–water, 60 : 40 (v/v).

[$HClO_4$] (M)	0·034	0·196	0·200	0·391	0·445	0·613	0·999
10^5k_1 (sec.$^{-1}$)	8·50 [a]	76·1 [b]	14·0	19·5	16·8 [c]	28·4	37·3

Dioxan–water, 40 : 60 (v/v).

[$HClO_4$] (M)	0·144	0·157	0·258	0·350	0·371	0·372	0·536	0·675
10^5k_1 (sec.$^{-1}$)	40·6	43·4 [a]	45·8	39·8 [e]	36·9 [d]	51·8	56·2	57·1

[a] Titrimetric method. [b] Temp. 25°. [c] [$LiClO_4$] = 0·567M. [d] [$LiClO_4$] = 0·585M. [e] [Et_4NBr] = 0·370M.

Iodometry was also used for hydrolyses in the presence of dilute perchloric acid, and dilatometry was satisfactory when the concentration of perchloric acid exceeded *ca.* 0·1M.

Alkaline hydrolysis by sodium hydroxide was too fast for conventional kinetic methods, but the reactions with sodium hydrogen carbonate or carbonate could be followed.

DISCUSSION

Consideration of the kinetic form and mechanism of these hydrolyses is simplified by the fact that only mechanisms of acyl–oxygen bond fission need to be considered (Table 1).

The marked effect of alkali on the hydrolysis shows that the mechanism here is $B_{Ac}2$. We can make no accurate comparison between the alkaline rates of this and other esters, because we do not know the concentrations of hydroxide ions in solutions of sodium carbonate or sodium hydrogen carbonate in aqueous dioxan. The rate is, as would be expected, greater with sodium carbonate. It is possible to make only a qualitative rate comparison between the alkaline hydrolyses of methyl acetate [11] and trifluoroacetate. The latter is considerably faster.

Hydrolyses of alkyl trifluoroacetates in initially neutral solutions are much faster than of unsubstituted carboxylic esters. Our values (Table 2) are similar to those found for

[11] Fairclough and Hinshelwood, *J.*, 1937, 538.

hydrolysis in aqueous acetone,[8] although the Arrhenius parameters differ for the two solvents. These parameters are in the range usually associated with bimolecular ester hydrolyses with acyl–oxygen fission,[12] and the rate increases with increasing water content of the solvent. All this evidence makes it most probable that here too the slow step of the reaction is nucleophilic attack of a water molecule on the acyl-carbon atom, by mechanism $B_{Ac}2$. We do not know whether bond-making and -breaking are synchronous, or whether an intermediate of finite life is formed by nucleophilic addition to the acyl-carbon atom of the ester molecule.[6]

The increase in rate observed during a run in initially neutral solution is an autocatalysis by trifluoroacetic acid, and the rate towards the end of a reaction is very close to that observed initially with a comparable amount of added trifluoroacetic acid (Table 2).

Neutral salts (lithium perchlorate and tetraethylammonium bromide) decrease the rate of hydrolysis in initially neutral solution. Kinetic effects of non-common ion salts on nucleophilic displacements on alkyl halides, or 'onium salts, in hydroxylic solvents can be explained in terms of changes in the size or distribution of charge during formation of the transition state. This simple theory is less satisfactory in ester hydrolyses where the nucleophilic reagent attacks a multipolar molecule. From the Brönsted equation we can write for the bimolecular neutral hydrolysis of an ester, E:

$$\text{Rate} \propto [\text{E}] \,.\, a_{\text{H}_2\text{O}} \,.\, f_{\text{E}}/f_{\text{T}^+}$$

(f_{E} and f_{T^+} are the activity coefficients of the initial and transition state respectively, and $a_{\text{H}_2\text{O}}$ is the activity of water.)

We know that many neutral salts " salt in " carboxylic esters,[13] *i.e.*, decrease their activity coefficients, though because of the rapid hydrolysis of alkyl trifluoroacetates this point cannot be tested here. It is also likely that salts will decrease the activity of water, and it seems that these salt effects on the reactants are the controlling factors in the neutral hydrolyses.

The acid hydrolyses were in general followed dilatometrically, although two control runs were done by the rather less accurate titrimetric method (Table 2). In all solvents the extent of acid-catalysis was small, very much less than usual for carboxylic-ester hydrolyses. The rate constant for a specific hydrogen-ion-catalysed reaction is made up of an equilibrium constant for the protonation of the neutral ester molecule, and a rate constant for the slow decomposition of the conjugate acid so formed. There is no reason why the decomposition should be slowed by the electron-withdrawing fluorine atoms, because it almost certainly involves a bimolecular attack by water molecules, and so we suppose that the small acid rate (relative to the neutral rate) is caused by a decrease in the basicity of the neutral ester molecule.

With increasing concentration of perchloric acid the rates tend to level off (see Figure), and a maximum is observed for the least aqueous solvent (although this is hardly outside the experimental error, see p. 3254). This levelling off is almost certainly not caused by complete protonation of the neutral molecule, as is sometimes found,[14] because a trifluoroacetate would be much too weak a base to be protonated fully in *ca.* M-perchloric acid in aqueous dioxan. It is a salt effect of the ions of perchloric acid, and decreases the rate of both acid-catalysed and neutral reactions.

This general behaviour is also found for the hydrolysis of phenyl trifluoroacetate (to be reported later). In this reaction a pronounced maximum is found and it also can be treated semi-quantitatively. It is here assumed that the " salt effects " of perchloric acid and lithium perchlorate are the same, and that the salt effect is proportional to concentration. These are oversimplifications. The relation between rate and ionic concentration usually follows an exponential equation, but use of this would make the

[12] Long and Pritchard, *J. Amer. Chem. Soc.*, 1957, **79**, 2365.
[13] Waind, *J.*, 1954, 2879.
[14] Evidence summarised by Long and Paul, *Chem. Rev.*, 1957, **57**, 954, 988.

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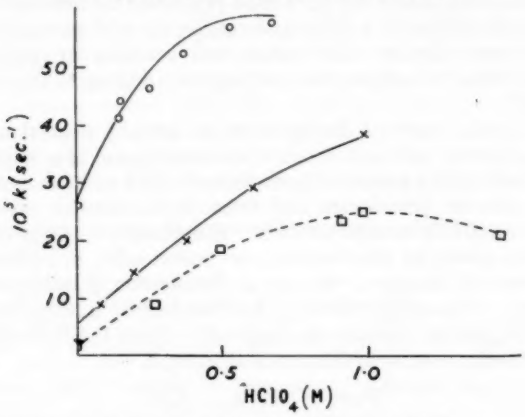
calculation excessively complicated, and for low concentrations of salts or acid the linear and exponential forms do not differ much.

Acid hydrolysis of methyl trifluoroacetate at 0°.



Full lines are calculated. ○ 40 : 60, × 60 : 40, □ 70 : 30 v/v *dioxan-water.*

The observed first-order rate constant k^0 can be separated into two terms, *e.g.*,

$$k^0 = k^0_n + k^0_a . C_a \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where C_a and C_s are the concentrations of the fully dissociated mineral acid and salt respectively, and k^0_n and k^0_a are:

$$k^0_n = k_n - p(C_s + C_a) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$k^0_a = k_a - q(C_s + C_a) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Here k_n and k_a are the rate constants for neutral and acid hydrolyses, respectively, at zero ionic concentration. When $C_s = 0$, equations 1, 2, and 3 give the quadratic equation:

$$k^0 = k_n + (k_a - p - qC_a)C_a \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The rate constant k_n is known, p can be evaluated from the salt effect on the neutral rate, and $(k_a - p)$ is the initial slope of the plot of rate constant against acid concentration. The remaining parameter q is evaluated by taking a point on the experimental plot and solving equation (4). The quadratic form of this equation predicts a maximum in the rate, and the calculated position is:

$$C_a(\text{max.}) = (k_a - p)/2q$$

The values so calculated are given below in the units for k^0 and k_n of 10^{-5} sec.$^{-1}$; for k_a and p, 10^{-5} sec.$^{-1}$ mole^{-1} l.; and for q, 10^{-5} sec.$^{-1}$ mole^{-2} l.^{2}; with C_a in mole l.$^{-1}$.

Dioxan–water, 40 : 60 v/v. Temp. 0°. $k_n = 25{\cdot}6$; $k_a = 127$; $p = 7{\cdot}9$; $q = 107$ (from $k^0 = 57{\cdot}1$ at $C_a = 0{\cdot}675$M). Calc. C_a max. = 0·56M.
Dioxan–water, 60 : 40 v/v. Temp. 0°. $k_n = 5{\cdot}45$, : $k_a = 47{\cdot}1$; $p = 1{\cdot}5$; $q = 13{\cdot}6$ (from $k^0 = 37{\cdot}5$ at $C_a = 1{\cdot}0$). Calc. C_a max. = 1·7M.

The rate constants for 70 : 30 v/v dioxan–water are not sufficiently accurate for evaluation of these constants, but here $10^5 k_a \approx 30$ (sec.$^{-1}$ mole^{-1} l.).

The second-order rate constants, k_a, for the acid-catalysed reaction decrease with decreasing water content of the solvent. This is, in fact, the order of the relative acidities as determined by indicator measurements,[15,16] suggesting that the determining factor for

[15] Braude and Sterne, *J.*, 1948, 1976.
[16] Bunton, Ley, Rhind-Tutt, and Vernon, *J.*, 1957, 2327.

the solvent effect on the acid reaction is the extent of protonation of the neutral ester molecule, rather than the rate of decomposition of the conjugate acid.

In formulating this picture of the kinetic form of acid hydrolysis we have assumed that the mechanism is $A_{Ac}2$. This is almost certainly correct, because we know the bond fission to be acyl–oxygen, and mechanism $A_{Ac}1$ is found only in highly ionising acidic solvents or with esters in which the acylium ion is stabilised by electron release.

Experimental

Materials.—Methyl trifluoroacetate was prepared by mixing trifluoroacetic acid with an excess of methanol at room temperature, and distilling off the ester through a 20 cm. helix-packed column. The ester, after refractionation, had b. p. 40°, and sap. equiv. 127·5. The purity was tested by passing the ester through a gas-phase chromatograph. The trace showed the presence of a minor peak of area *ca.* 1/1000 that of the main peak. A b. p. of 43° has been reported for this ester.[8, 17]

Kinetic Measurements.—The solvent was aqueous dioxan, containing 40%, 60%, or 70% of purified dioxan (v/v).

The conventional method for following an ester hydrolysis, by acid–base titration, could not be used, because the ester reacts very rapidly with hydroxide ions. Three methods were used.

(1) *Titrimetric method.* Portions (5 c.c.) of the reaction mixture were added to ice-cold 70% acetone (30 c.c.) containing a solution (1—4 c.c.) of potassium iodide (0·03M) and potassium iodate (0·15M). The iodine liberated was titrated quickly with 0·01N-sodium thiosulphate; no indicator was used: $6H^+ + 5I^- + IO_3^- \longrightarrow 3I_2 + 3H_2O$. This method was not very accurate but could be used for runs in initially neutral or dilute acid solutions. An example is given:

Solvent, dioxan–water 60 : 40 v/v. Temp. 0°. The concentration units are in c.c. of 0·01N-sodium thiosulphate per 5 c.c. portions.

Time (min.)	0		15	20	30	40	60·5	75	∞	
$[CF_3{\cdot}CO_2H]$	3·30	3·70	8·20	9·50	12·30	14·70	18·75	20·40	29·25	29·70

$10^5k_1 = 23{\cdot}6$ (sec.$^{-1}$) obtained graphically from the usual first-order integrated rate equation.

This iodometric method was not used for the runs with sodium carbonate or hydrogen carbonate. In these, portions (5 c.c.) were titrated rapidly with 0·05N-hydrochloric acid (methyl-orange). An example is given with values for the half-lives of other experiments:

Dioxan–water 40 : 60 v/v.
Initially $[Na_2CO_3] = 0{\cdot}076$N, $[CF_3{\cdot}CO_2Me] = 0{\cdot}047$M, temp. 0°.

Time (min.)	0	1	3	5·5	6·75	10	15	20
Titre (c.c.)	7·55	3·72	3·35	3·30	3·22	3·08	2·87	2·83

Initially $[NaHCO_3] = 0{\cdot}070$N, $[CF_3{\cdot}CO_2Me] = 0{\cdot}047$M, temp. 0°: $t_{\frac{1}{2}} = 7{\cdot}25$ min.
Initially $[NaHCO_3] = 0{\cdot}093$N, $[CF_3{\cdot}CO_2Me] = 0{\cdot}071$M, temp. 0°: $t_{\frac{1}{2}} = 7{\cdot}5$ min.
Initially $[NaHCO_3] = 0{\cdot}089$N, $[CF_3{\cdot}CO_2Me] = 0{\cdot}058$M, temp. 15°: $t_{\frac{1}{2}} \sim \frac{1}{4}$ min.

If sodium hydroxide is added to a solution of the ester at 0° the end-point drifts continuously. We tried to follow the reaction by mixing a solution of the ester with one of sodium hydroxide, and then quickly quenching the reaction by adding an excess of hydrochloric acid. This was unsuccessful; probably the rate of mixing was the limiting factor.

(2) *Conductance method.* This is very sensitive, but is suitable only for hydrolyses in initially neutral solution. The conductivity of trifluoroacetic acid in the kinetic solvents was first measured. A sample of the values so obtained is given below.

Dioxan–water 60 : 40 v/v, temp. 0°.								
$[CF_3{\cdot}CO_2H]$ (10^{-3}M)	0·107	0·540	0·820	1·90	3·74	8·20	13·12	16·82
Λ (ohm^{-1} cm.^{2})	50·5	47·2	43·7	37·6	32·6	27·3	23·6	21·5
Dioxan–water 60 : 40 v/v, temp. 25°.								
$[CF_3{\cdot}CO_2H]$ (10^{-3}M)	0·73	1·90	3·94	5·36	6·84	8·32	9·95	11·53
Λ (ohm^{-1} cm.^{2})	70·3	56·7	48·2	44·1	41·6	39·1	37·3	35·5
Dioxan–water 40 : 60 v/v, temp. 0°.								
$[CF_3{\cdot}CO_2H]$ (10^{-3}M)	0·182	0·389	1·61	3·10	5·47	6·71	8·37	9·98
Λ (ohm^{-1} cm.^{2})	99·4	97·0	87·6	77·8	65·5	59·6	52·7	47·2

[17] Gryszkiewicz-Trochimowski, Sporzyński, and Wnuk, *Rec. Trav. chim.*, 1947, **66**, 413.

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The changes in conductivity during reaction were converted into changes in the concentration of the trifluoroacetic acid. This was essential because the acid is only partially dissociated in aqueous dioxan, and the degree of dissociation varies with the concentration. The alternate points of a run followed by this method are given below:

Dioxan–water 60 : 40 v/v, temp. 25°.

Time (min.)	10	20	30	40	56	79	92	110	∞
$[CF_3{\cdot}CO_2H]$ (10^{-2}M)	1·16	2·15	2·97	3·75	4·70	5·78	6·20	6·70	7·90

Initial $10^5k_1 = 24{\cdot}6$ (sec.$^{-1}$).

(3) *Dilatometry.* This method was used for the neutral and acid hydrolyses. The results for the neutral hydrolyses were consistent among themselves, but not with those of the other methods. The rates were 30—40% higher (Table 2). This discrepancy comes from an inherent defect in the dilatometric method, which makes it unreliable for reactions such as these. It is assumed, in the use of the dilatometric method, that the percentage volume change during reaction is equal to the percentage reaction. This assumption is usually correct, but not in the hydrolysis of an alkyl trifluoroacetate in initially neutral solution. The volume change during reaction is caused by disappearance of ester and water and formation of alcohol and trifluoroacetic acid. The acid is only partially dissociated, and the greater part of the volume change caused by trifluoroacetic acid comes from interaction between its protons and solvent molecules. Therefore the volume change will depend upon the degree of dissociation of the acid, and this, and the volume change per unit of reaction, will change during the reaction. We should expect the volume change for a given amount of reaction to be greatest at the beginning of a run, when the concentration of trifluoroacetic acid is low and its degree of dissociation high. Thus the rates measured dilatometrically should be too high, as is found. The logarithmic plot, as used,[18] would be too insensitive to detect trends during reaction. Although the method does not give correct results in initially neutral solution it is satisfactory in the presence of perchloric acid in concentration sufficient to buffer the hydrogen-ion concentration and so keep the degree of dissociation constant during a run. From the dissociation constants of trifluoroacetic acid determined during this work we can calculate the change in the degree of dissociation (α) during a kinetic run.

Dioxan–water 40 : 60 v/v.

$[HClO_4]$ (M)	$[CF_3{\cdot}CO_2H]$ (M) =	0·01	0·05	$\Delta\alpha$
		α		
0·0		0·95	0·83	0·12
0·2		0·50	0·47	0·03
0·3		0·40	0·39	0·01
0·4		0·33	0·33	0·00

Dioxan–water 60 : 40 v/v.

$[HClO_4]$ (M)	$[CF_3{\cdot}CO_2H]$ (M) =	0·01	0·05	$\Delta\alpha$
		α		
0·0		0·79	0·53	0·26
0·1		0·23	0·21	0·02
0·2		0·13	0·13	0·00

These calculations are approximate, because activity effects are neglected, but they show that the dilatometric method is likely to give the wrong answer in initially neutral solution. They also suggest that it is reliable when sufficient perchloric acid is present. Dilatometry should be satisfactory for reactions with acid products when the acid is either weak or very strong; the difficulties arise here because trifluoroacetic acid, in aqueous dioxan, is of intermediate strength. The suppression of the dissociation of trifluoroacetic acid imposes another limit on the method, because with increasing perchloric acidity the volume change (a contraction at all acidities in the two more aqueous solvents) becomes too small. Our experiments were taken to this limit with some loss of accuracy at the higher acidities. In 70 : 30 v/v dioxan–water the usual contraction, decreasing with acidity, is replaced by a small expansion at perchloric acidities >0·8M. This behaviour is real and independent of the dilatometer; presumably at higher acidities the contraction during reaction which comes from the interaction between protons and solvent molecules becomes less than the expansion caused by the formation of two product molecules from one ester molecule. We estimate that the accuracy of the dilatometric runs with $[HClO_4]$ <0·5M is 2%. At higher perchloric acidities (*ca.* M) the accuracy is reduced to 5%.

Bond Fission.—Homogeneous conditions. The solvent was 60 : 40 v/v dioxan–water, with the water enriched in ^{18}O. After complete reaction under kinetic conditions at 25° dry potassium carbonate was added, and the non-aqueous layer separated and dried over more potassium

[18] Guggenheim, *Phil. Mag.*, 1926, **2**, 538.

carbonate. It was then distilled and the first portion of the distillate fractionated through a 12" column packed with a metal spiral. The methanol so obtained had a high refractive index, n_D^{25} *ca.* 1·33, and was probably contaminated with a small amount (<4%) of dioxan.

Heterogeneous conditions. The ester was completely hydrolysed in isotopically enriched water, with vigorous stirring, at 25°. The final solution was neutralised with aqueous sodium hydroxide, and the methanol was distilled off and purified by fractionation as already described. The isotopic abundances of the methanol samples were determined by pyrolysis to carbon monoxide and mass-spectrometric analysis of this gas.

Appendix

Dissociation Constants in Aqueous Dioxan.—The usual method for determination of acid dissociation constants, that of conductivity,[19] was not very suited to our system, because it requires a reliable value for Λ_0, and it was difficult to determine this in aqueous dioxan. Therefore an indicator method was used; the values so obtained were in agreement with approximate values calculated from our conductivity data.

The dissociation constant of purified *m*-nitroaniline in perchloric acid in aqueous dioxan at 15° was first determined spectrophotometrically, at 370, 375, and 380 mμ in 60 : 40 v/v dioxan–water, and 365, 370, and 375 mμ in 40 : 60 v/v dioxan–water. The indicator ratio, $r = [BH^+]/[B]$, where B is *m*-nitroaniline, was determined for a series of perchloric acidities; the ratio $r/[H^+]$, extrapolated to zero concentration of perchloric acid, gave the thermodynamic dissociation constant K_b. All measurements were at room temperature:

In 40 : 60 v/v dioxan–water, $K_b = 38{\cdot}7$ (mole^{-1} l.).

In 60 : 40 v/v dioxan–water, $K_b = 12{\cdot}5$ (mole^{-1} l.).

The indicator ratios can then be determined in trifluoroacetic acid solutions, giving the apparent hydrogen-ion concentration, and so the dissociation constant. These classical dissociation constants, K_c, extrapolated to zero acid concentration, give the thermodynamic dissociation constants K_a.

Dioxan–water 40 : 60 v/v:					
$[CF_3{\cdot}CO_2H]$ (10^{-2}M)	2·14	4·27	6·41	8·55	10·7
r (average)	0·727	1·39	1·94	2·45	2·68
$[H^+]$ (10^{-2}M)	1·95	3·66	5·10	6·38	6·95
Degree of dissocn.	0·912	0·857	0·795	0·746	0·650
K_c (10^{-1} mole l.$^{-1}$)	2·00	2·19	1·99	1·92	1·29

$K_a = 0{\cdot}21$ (mole l.$^{-1}$)

Dioxan–water 60 : 40 v/v.					
$[CF_3{\cdot}CO_2H]$ (10^{-2}M)	2·13	4·26	6·38	8·51	10·64
r (average)	0·166	0·293	0·401	0·500	0·606
$[H^+]$ (10^{-2}M)	1·30	2·34	3·25	4·09	5·04
Degree of dissocn.	0·61	0·55	0·51	0·48	0·47
K_c (10^{-2} mole l.$^{-1}$)	2·04	2·85	3·37	3·78	4·54

$10^2K_a = 1{\cdot}5$ (mole l.$^{-1}$).

These values show that the dissociation constant decreases sharply with decreasing water content, *e.g.*, the values in water are 0·588 (mole l.$^{-1}$) at 25° and 0·533 at 35°.[20]

It is known that the dissociation constant of hydrochloric acid decreases with decreasing water content of an aqueous-dioxan solvent. Thus the dissociation[21] in 40% dioxan (by wt.) is *ca.* 1, in 70% it decreases to $7{\cdot}7 \times 10^{-3}$ (mole l.$^{-1}$), and in 82% to $2{\cdot}02 \times 10^{-4}$ at 25°. From an interpolation of these values it seems that in our aqueous dioxan solvents hydrochloric acid has a dissociation constant *ca.* 5 times that of trifluoroacetic acid.

Pierce and Gorrin[10] measured the relative strengths of hydrochloric and trifluoroacetic acid in water and in 70 : 30 v/v acetone–water, from their catalytic effects on the hydrolysis rate of ethyl acetate. The rates for a given acid concentration are identical in water, but that with hydrochloric acid is *ca.* 2½ times greater in the mixed solvent. Thus the solvent

[19] Harned and Owen, "Physical Chemistry of Electrolytic Solutions," Reinhold Publ. Corp., New York, 1950.
[20] Henne and Fox, *J. Amer. Chem. Soc.*, 1951, **73**, 2323.
[21] Owen and Walters, *ibid.*, 1938, **60**, 2371.

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" levelling " effect of water makes trifluoroacetic acid almost fully dissociated in dilute aqueous solution; this effect has disappeared in aqueous acetone, and in these aqueous–organic solvents trifluoroacetic acid is not a strong acid.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, GOWER STREET,
LONDON, W.C.1.

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666. *Cyclic Organic Boron Compounds. Part II.*[1] *Chemical Properties of* n-*Butyl Metaborate.*

By M. F. LAPPERT.

n-Butyl metaborate $(Bu^nO{\cdot}BO)_3$ is highly reactive, with affinity for reagents having nucleophilic activity (water; butan-1-ol; hydrogen, phosphorus, boron, and thionyl halides; carboxylic acids, chlorides, and anhydrides; and amines).

IN Part I the preparation, physical properties, structures, and thermal and hydrolytic stability of a number of alkyl and phenyl metaborates were described.[1] The present paper concerns the chemical properties of the *n*-butyl homologue, which is regarded as typical of the alkyl compounds. For convenience, the empirical formula BuO·BO is used in the succeeding equations, in place of boroxole structure [1,2] $(BuO{\cdot}BO)_3$.

Reactions here reported are: with water or butan-1-ol to give butyl borate and boric acid; with non-metal halides to give butyl halides; with acids, acid chlorides, or anhydrides to give butyl esters; with boron trifluoride or trichloride to give butyl dihalogenoboronite; and with amines to give complex compounds. The metaborate did not react, under stated conditions, with *n*-butyl chloride, di-*n*-butyl ether, or hydrogen chloride; with propionamide, there was some dehydration to give propionitrile.

In the reactions with water and butan-1-ol there was no evidence that intermediate hydrogen or dihydrogen orthoborate had formed, although (−)-menthyl dihydrogen orthoborate has previously been obtained.[3] Hydrolysis to butan-1-ol and orthoboric acid was complete when a larger amount of water was used.

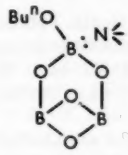
Hydrogen bromide did not react with the metaborate at 20°/760 mm., but dealkylation was rapid when the reaction was carried out under pressure; the observation is consistent with a mechanism involving rate-determining S_N2 attack of Br^- on the protonated metaborate. A similar concentration effect has previously been noted with alkyl diphenylboronites, $RO{\cdot}BPh_2$.[4]

Phosphorus penta-chloride and -bromide reacted readily and exothermally with the metaborate at 20°, but under similar conditions phosphorus trichloride and thionyl chloride did not, except in the presence of a trace of ferric chloride. In every case, the butyl chloride product contained 5—10% of the *sec.*-isomer; boron trioxide was invariably obtained together with phosphorus oxyhalide, phosphorus trioxide, or sulphur dioxide, respectively, in the several systems. The partial molecular rearrangement of the *n*-butyl group suggests that *n*-butyl carbonium ions are formed, which then undergo Wagner–Meerwein rearrangement. This suggestion would be consistent with the observed ferric chloride catalysis, as electrophilic catalysis of S_N1 reactions is general.[5] Catalysis by ferric chloride (and other Lewis acids) has previously been noted in certain other organic

[1] Lappert, *J.*, 1958, 2790.
[2] *Idem, Chem. Rev.*, 1956, **56**, 959.
[3] O'Connor and Nace, *J. Amer. Chem. Soc.*, 1955, **77**, 1578.
[4] Abel, Gerrard, and Lappert, *J.*, 1957, 3833.
[5] Ingold, " Structure and Mechanism in Organic Chemistry," p. 375, Bell and Sons, London, 1953.

boron systems.[6,7,8] Although the rearrangement *n*-butyl ⟶ *sec.*-butyl is not well known, it is likely that it has frequently not been detected in the past because of the lack of adequate methods of analysis, particularly gas chromatography.

With acetyl and benzoyl chloride (heating; no reaction at 20°), the *n*-butyl carboxylate formation was accompanied by that of boron trioxide and butyl chloride (90—95% *n*- and 5—10% *sec.*-). The formation from a metaborate of a carboxylic ester, by reaction with its parent acid (here demonstrated for R = Me or Ph), anhydride (R = Me), or acid chloride may prove to be of preparative value for esters which are not readily prepared by more direct methods.



(I)

The addition of pyridine to *n*-butyl metaborate instantly produced a white complex: $4Bu^nO{\cdot}BO + C_5H_5N \longrightarrow Bu^nO{\cdot}B_3O_4,NC_5H_5 + B(OBu^n)_3$. It was insoluble in organic solvents but was readily hydrolysed by cold water to give pyridine, butan-1-ol, and orthoboric acid. When heated it readily lost pyridine, and eventually butene and butan-1-ol. Other amines (Bu^nNH_2, Et_2NH, and Et_3N) reacted similarly, but precipitation of the complexes was much slower. For example, with *n*-butylamine, the reaction was not complete after 3 weeks at 20°. The complex may be formulated as (I) or as a polymer, formed by opening of the four-membered ring.

The present results should be compared with established reactions for other boroxoles [*e.g.*, $(Bu^n{\cdot}BO)_3$] and orthoborates [*e.g.*, $B(OBu^n)_3$].[2,4,9]

Experimental

General Procedures.—*n*-Butyl metaborate was prepared from boron trioxide.[1] In addition to constants and standard analytical procedures,[6,10] gas chromatography was used for both qualitative and quantitative analysis of all products having b. p. <140°/760 mm.

Hydrolysis and Alcoholysis.—Water (0·56 g.) in diethyl ether (10 c.c.) was added to the metaborate (3·11 g.) at 20°. A white precipitate (1·061 g.) was formed instantly and was filtered off. Removal of solvent from the filtrate afforded more precipitate, which was separated by addition of *n*-pentane (20 c.c.) and filtration. The combined precipitate was identified as orthoboric acid (1·273 g., 100%) (Found: B, 17·1. Calc. for H_3O_3B: B, 17·5%); the filtrate afforded tri-*n*-butyl borate (1·76 g., 74%), b. p. 110—114°/12 mm., n_D^{20} 1·4103 (Found: B, 4·70. Calc. for $C_{12}H_{27}O_3B$: B, 4·72%). Yields are based on: $3Bu^nO{\cdot}BO + 3H_2O \longrightarrow B(OBu^n)_3 + 2B(OH)_3$.

By similar technique, addition of *n*-butyl alcohol (1·85 g.) to the metaborate (2·55 g.) afforded orthoboric acid (0·462 g., 88%) and the orthoborate (3·41 g., 87%), b. p. 112°/10 mm., n_D^{20} 1·4100. Yields are based on: $3Bu^nO{\cdot}BO + 3Bu^nOH \longrightarrow 2B(OBu^n)_3 + B(OH)_3$.

Hydrogen Halides.—The metaborate did not react with gaseous hydrogen chloride at 20° even in presence of ferric chloride.

Liquid hydrogen bromide (4·61 g.) and the metaborate (2·03 g.) were mixed at −80° and the vessel was sealed. Within 30 min. at 20° the mixture set to an opaque solid. After 24 hr. at 20°, the vessel was opened at −80°, and unchanged hydrogen bromide was allowed to escape, whereafter volatile matter was condensed at 20°/10 mm. into a trap at −80°. The condensate was distilled from lead carbonate and dried ($CaCl_2$); redistillation gave *n*-butyl bromide (1·84 g., 66%), b. p. 95—98°/760 mm., n_D^{20} 1·4403. The residue (1·34 g.) contained boron, equivalent to metaboric acid (0·833 g., 94%). Yields are based on: $Bu^nO{\cdot}BO + HBr \longrightarrow Bu^nBr + HO{\cdot}BO$.

[6] Lappert, *J.*, 1956, 1768.
[7] Gerrard and Lappert, *J.*, 1955, 3084.
[8] Brindley, Gerrard, and Lappert, *J.*, 1956, 1540; Dandegaonker, Gerrard, and Lappert, *J.*, 1957, 2872.
[9] Abel, Dandegaonker, Gerrard, and Lappert, *J.*, 1956, 4697; Dandegaonker, Gerrard, and Lappert, *J.*, 1957, 2893; Gerrard, Lappert, and Shafferman, *ibid.*, p. 3828; McCusker and Glunz, *J. Amer. Chem. Soc.*, 1955, **77**, 4253; McCusker, Ashby, and Makowski, *ibid.*, 1957, **79**, 5182; McCusker and Makowski *ibid.*, p. 5185.
[10] Gerrard and Lappert, *J.*, 1951, 2545; Gerrard, Lappert, and Silver, *J.*, 1956, 3285; 1957, 1647; Abel, Edwards, Gerrard, and Lappert, *J.*, 1957, 501.

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Boron Trihalides.—When boron trifluoride was passed into the metaborate in absence of solvent, working-up was difficult owing to incomplete reaction caused by gelation. Accordingly, the gas was passed through the ester (5·00 g.) in *n*-pentane (25 c.c.), whereupon precipitation of a white solid was rapid. Solvent was removed at 20°/20 mm., and distillation gave *n*-butyl difluoroboronite (4·42 g., 73%), b. p. 45—48°/10 mm., n_D^{14} 1·3882, which was also characterised by comparing its infrared spectrum with that of an authentic specimen.[11] The white, solid distillation residue (2·12 g.) was washed with diethyl ether to give, as an amorphous powder, boron trioxide (1·13 g., 97%) (Found: B, 30·6. Calc. for O_3B_2: B, 31·1%).

Boron trichloride (3·00 g.) was added to the metaborate (1·73 g.) at −80°. Matter volatile at 20°/1 mm. was condensed into a trap at −80°. The condensate was twice distilled, giving *n*-butyl dichloroboronite (1·34 g., 50%), b. p. 40—42°/20 mm., n_D^{20} 1·4142 (Found: Cl, 44·8; B, 6·8. Calc. for $C_4H_9OCl_2B$: Cl, 45·8; B, 7·0%). The distillation residue (2·28 g.) was a fuming white solid and appeared to be impure boron oxychloride.

Phosphorus Pentahalides.—When phosphorus pentachloride (11·36 g.) and the metaborate (5·45 g.) were mixed, an exothermal reaction took place. The mixture was set aside for 24 hr. at 15°, whereafter matter volatile at 20°/0·01 mm. was condensed into a trap at −80°. The condensate (10·74 g.) was a mixture of butyl chlorides (90—95% of *n*- and 5—10% of *sec.*-butyl) (2·94 g., 59%) and phosphorus oxychloride (7·80 g., 93%). The residue (5·24 g.) contained boron, equivalent to boron trioxide (1·90 g., 100%). Yields are based on: $Bu^nO{\cdot}BO + PCl_5 \longrightarrow Bu^nCl + POCl_3 + [BOCl]$.

Similarly, from the pentabromide (6·20 g.) and the metaborate (1·46 g.), there was obtained a mixture of butyl bromides (1·20 g., 61%), b. p. 80—100°/760 mm., n_D^{20} 1·4393, separated from other products by aqueous treatment.

Phosphorus Trichloride.—The trichloride (4·75 g., 1 mol.) and the metaborate (3·46 g., 1 mol.) were mixed at 20° and set aside for 72 hr.; there was no sign of reaction. Ferric chloride (0·050 g.) was added and after 4 hr. at 20° the mixture became gelatinous and after 24 hr. semi-solid. It was then heated under reflux for 1 hr. and subsequent distillation afforded a mixture of phosphorus trichloride (3·20 g., 0·675 mol.) and butyl chloride (90—95% of *n*- and 5—10% of *sec.*-butyl) (2·63 g., 82%), b. p. 72—78°/760 mm., n_D^{21} 1·4627. There was a white residue (2·22 g.), which contained boron, equivalent to boron trioxide (1·20 g., 99%), and phosphorus, equivalent to phosphorus trioxide (0·632 g., 100%). Yields are based on: $6Bu^nO{\cdot}BO + 2PCl_3 \longrightarrow 6Bu^nCl + 3B_2O_3 + P_2O_3$.

Thionyl Chloride.—The metaborate did not react with thionyl chloride under reflux during 3½ hr.

A mixture of the metaborate (3·01 g.), thionyl chloride (3·52 g.), and ferric chloride (0·033 g.) was heated under reflux for 1 hr. Distillation afforded a mixture of thionyl chloride (1·36 g.) and butyl chloride (90—95% of *n*- and 5—10% of *sec.*-butyl) (1·80 g., 65%), b. p. 68—78°/760 mm., n_D^{22} 1·4358. There was a residue (1·65 g.), which contained boron, equivalent to boron trioxide (1·01 g., 95%). During the work-up, sulphur dioxide was evolved. Yields are based on: $2Bu^nO{\cdot}BO + SOCl_2 \longrightarrow 2Bu^nCl + B_2O_3 + SO_2$.

Acetyl Chloride.—The metaborate (3·38 g., 1 mol.) and acetyl chloride (2·66 g., 1 mol.) were set aside for 24 hr. at 20°; there was no sign of reaction. The whole was then heated under reflux for 4 hr. and on cooling became solid. A condensate comprising a mixture of acetyl chloride (1·07 g.), *n*-butyl acetate (2·84 g., 64%), and butyl chloride (90—95% *n*- and 5—10% *sec.*-butyl) (0·56 g.), n_D^{20} 1·3962, was obtained by heating at 110°/1 mm. There was a residue (1·33 g.), containing boron, equivalent to boron trioxide (1·12 g., 95%).

Benzoyl Chloride.—Similarly, when the metaborate (1·55 g., 2 mols.) and benzoyl chloride (1·09 g., 1 mol.) were mixed there appeared to be no reaction. After heating, under reflux, for 4 hr., distillation afforded *n*-butyl benzoate (1·32 g., 96%), b. p. 70—72°/0·01 mm., n_D^{22} 1·4962, and a residue (0·58 g.), containing boron, as the trioxide (0·540 g., 99%). There was a condensate of *n*- (90—95%) and *sec.*-butyl chloride (5—10%) (0·59 g., 83%). Yields are based on: $2Bu^nO{\cdot}BO + Ph{\cdot}COCl \longrightarrow Bu^nCl + Bu^nO{\cdot}COPh + B_2O_3$.

Acetic Anhydride.—There was no heat of mixing when acetic anhydride (1·34 g.) was added to the metaborate (2·73 g.) at 20°, but after ½ hr. under reflux there was obtained *n*-butyl acetate (2·54 g., 80%), b. p. 120—122°/760 mm., n_D^{20} 1·3936, and a white residue (1·23 g.), which contained boron, equivalent to boron trioxide (0·953 g., 100%). Yields are based on: $2Bu^nO{\cdot}BO + (CH_3{\cdot}CO)_2O \longrightarrow 2Bu^nO{\cdot}CO{\cdot}CH_3 + B_2O_3$.

[11] Lappert, *J.*, 1955, 784.

Carboxylic Acids.—A mixture of acetic acid (1·54 g.) and the metaborate (2·57 g.) was heated under reflux for 2 hr. Distillation afforded a mixture of *n*-butyl acetate (2·22 g., 66%) and acetic acid (0·635 g.), b. p. 124—126°/760 mm., n_D^{20} 1·3892. There was a white solid residue (1·17 g.) containing boron, equivalent to metaboric acid (1·12 g., 100%).

A mixture of benzoic acid (1·12 g.) and the metaborate (0·915 g.) was heated under reflux for 3 hr. at 150°. Distillation afforded *n*-butyl benzoate (1·10 g., 62%), b. p. 120°/10 mm., n_D^{20} 1·4973, and a white solid residue (0·76 g.) containing boron, equivalent to metaboric acid (0·615 g. Calc. for HO·BO: 0·401 g.). Yields are based on: $Bu^nO{\cdot}BO + R{\cdot}CO_2H \longrightarrow Bu^nO{\cdot}COR + HO{\cdot}BO$.

Amines.—Pyridine (1·20 g.) was added to the metaborate (5·14 g.) in *n*-pentane (20 c.c.) at 20°. Reaction was slightly exothermal and a voluminous white precipitate was immediately formed. Filtration afforded the *complex* (3·165 g., 99%) (Found: C, 43·1; H, 5·60; C_5H_5N, 31·4; B, 13·2. $C_9H_{14}O_5NB_3$ requires C, 43·4; H, 5·62; C_5H_5N, 31·8; B, 13·1%) and from the filtrate there was obtained tri-*n*-butyl borate (2·60 g., 88%), b. p. 105—107°/12 mm., n_D^{23} 1·4082 (Found: C, 62·2; H, 11·7; B, 4·7. Calc. for $C_{12}H_{27}O_3B$: C, 62·7; H, 11·7; B, 4·7%). The complex was insoluble in *n*-pentane, diethyl ether, methylene dichloride, *cyclo*hexane, camphor, benzene, and nitrobenzene.

In a similar manner, from diethylamine (0·63 g.) and metaborate (3·45 g.) in *n*-pentane (20 c.c.), there was formed the diethylamine *complex* (1·692 g., 81%) (Found: Et_2NH, 25·9; B, 13·2. $C_8H_{20}O_5NB$ requires Et_2NH, 26·8; B, 13·4%), tri-*n*-butyl borate (1·74 g., 88%), b. p. 104—110°/9 mm., n_D^{20} 1·4110 (Found: B, 4·8%), and a residue (0·52 g.). This reaction differed from the pyridine system in that precipitation of the complex was incomplete even after the mixture had been kept at 48 hr. at 20°.

Similar results were obtained with triethylamine and *n*-butylamine, as already described.

Other Reagents.—There was no reaction between the metaborate and *n*-butyl chloride at 20° during 4 days or di-*n*-butyl ether under reflux during 6 hr.

A mixture of propionamide (1·63 g.) and the metaborate (4·47 g.) was heated at 220° for 48 hr. in a sealed tube. The tube was opened and heated for 1 hr. at 220°/0·1 mm. There was a condensate (2·58 g.), trapped at −80°, which on distillation afforded a fraction (1·69 g.), b. p. 100—130°/760 mm., which contained propionitrile (10—15%).

The author thanks Mr. H. Pyszora for the infrared spectral measurements and the National College of Rubber Technology (Northern Polytechnic) for providing facilities for these. He also gratefully acknowledges continued encouragement by Dr. W. Gerrard.

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667. *The Skraup Reaction with Aminopyrazoles.*

By I. L. FINAR and R. J. HURLOCK.

4-Amino-1-phenylpyrazole has been converted by the Skraup reaction into 1′-phenylpyrazolo(4′ : 5′-2 : 3)pyridine the structure of which has been proved by synthesis and ultraviolet absorption spectroscopy. Some pyrazolylquinolines have also been prepared from 1-aminophenylpyrazoles by the Skraup reaction.

4-AMINO-1-PHENYLPYRAZOLE, previously obtained from glucosazone,[1] was more conveniently prepared by the reduction of 4-nitro-1-phenylpyrazole[2] with hydrazine hydrate and palladised charcoal.[3] Two isomers can theoretically be obtained from this amine in the Skraup reaction, by ring closure in the 5- or the 3-position of the pyrazole ring to give compound (I or II; R = H).

Attempts to cause ring closure with 75% and 85% sulphuric acid[4] and arsenic pentoxide as oxidising agent failed; small amounts of unchanged amine were recovered.

[1] Heubner and Link, *J. Amer. Chem. Soc.*, 1950, **72**, 4812.
[2] Finar and Hurlock, *J.*, 1957, 3024.
[3] Dewar and Mole, *J.*, 1956, 2556.
[4] B.P. 394,416/1933.

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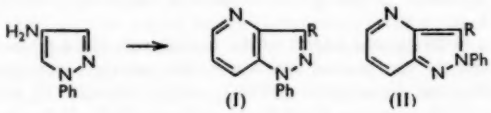
Ring closure, however, was achieved with concentrated sulphuric acid, and to give 1′-phenylpyrazolo(4′ : 5′-2 : 3)pyridine (I; R = H). The yield was only 2%, but a higher yield (19%) was obtained by using nitrobenzene as oxidising agent instead of arsenic pentoxide.

The structure of 1′-phenylpyrazolo(4′ : 5′-2 : 3)pyridine was established as follows. 3′-Methyl-1′-phenylpyrazolo(4′ : 5′-2 : 3)pyridine (I; R = Me) was prepared by the

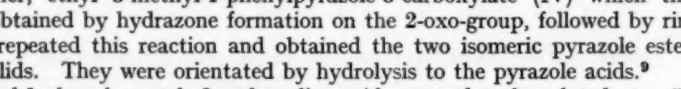


Skraup reaction with 4-amino-3-methyl-1-phenylpyrazole, ring closure being forced into position 5 by the 3-methyl group. The ultraviolet absorption curves of the two products between 210 and 350 mμ (*c* 0·03 in EtOH) were almost identical (R = H: $\lambda_{max.}$ 250 mμ, ε 2·2. R = Me: $\lambda_{max.}$ 271 mμ, ε 2·21). The general shape of the curves corresponds reasonably with published curves for 1-methylindazole derivatives but not with those for 2-methylindazole derivatives.[5] Thus the Skraup product from 4-amino-1-phenylpyrazole is 1′-phenylpyrazolo(4′ : 5′-2 : 3)pyridine (I; R = H).

4-Amino-3-methyl-1-phenylpyrazole, previously obtained by reduction of 4-amino-5-chloro-3-methyl-1-phenylpyrazole,[6] was prepared as follows: 4 : 4-Dimethoxybutan-2-one[7] was condensed with *p*-nitrophenylhydrazine, to give 3-methyl-1-*p*-nitrophenylpyrazole.[8] This was nitrated with mixed acids at 22° to give 3-methyl-4-nitro-1-*p*-nitrophenylpyrazole, which, on reduction in ethanol with ammonium hydrogen sulphide, gave 1-*p*-aminophenyl-3-methyl-4-nitropyrazole (cf. Finar and Hurlock[2]). This compound was diazotised and treated with hypophosphorous acid, to give 3-methyl-4-nitro-1-phenylpyrazole which, on reduction with hydrazine hydrate and palladised charcoal, gave 4-amino-3-methyl-1-phenylpyrazole.

An attempt was then made to synthesise the homologue of (II; R = Me) from 4-amino-5-methyl-1-phenylpyrazole. This amine was synthesised as follows: According to Claisen,[9] ethyl 2 : 4-dioxopentanoate condenses with phenylhydrazine to give ethyl 5-methyl-1-phenylpyrazole-3-carboxylate (III) as an oil. Claisen did not obtain the other isomer, ethyl 3-methyl-1-phenylpyrazole-5-carboxylate (IV) which theoretically could be obtained by hydrazone formation on the 2-oxo-group, followed by ring closure. We have repeated this reaction and obtained the two isomeric pyrazole esters as low-melting solids. They were orientated by hydrolysis to the pyrazole acids.[9]

5-Methyl-1-phenylpyrazole-3-carboxylic acid was decarboxylated to 5-methyl-1-phenylpyrazole which with mixed nitrating acids at 22° gave 5-methyl-4-nitro-1-*p*-nitrophenylpyrazole. This was reduced in ethanol with ammonium hydrogen sulphide to 1-*p*-aminophenyl-5-methyl-4-nitropyrazole, which was diazotised and treated with



hypophosphorous acid. 5-Methyl-4-nitro-1-phenylpyrazole, thus obtained, was reduced to 4-amino-5-methyl-1-phenylpyrazole. The Skraup reaction with this amine failed.

[5] Rousseau and Lindwall, *J. Amer. Chem. Soc.*, 1950, **72**, 3047.
[6] Michaelis and Schäfer, *Annalen*, 1915, **407**, 238.
[7] Hata, Yamada, Iwao, Kato, Sugimoto, and Inouye, *J. Pharm. Soc. Japan*, 1949, **69**, 477; *Chem. Abs.*, 1950, **44**, 3455.
[8] Burness, *J. Org. Chem.*, 1956, **21**, 97.
[9] Claisen, *Annalen*, 1894, **278**, 269.

Unchanged material was recovered, together with a small amount of quinoline obtained as a by-product from the nitrobenzene present (cf. Das Gupta [10]).

1-*p*-Aminophenylpyrazole, prepared from 1-*p*-nitrophenylpyrazole by reduction with hydrazine hydrate and palladised charcoal, was heated with glycerol, 60% sulphuric acid, and arsenic pentoxide. 6-1′-Pyrazolylquinoline was obtained; 1-*p*-aminophenyl-4-nitropyrazole under the same conditions gave 6-(4-nitro-1-pyrazolyl)quinoline. Both amines were destroyed in the Skraup reaction when concentrated sulphuric acid was used.

Experimental

The light petroleum had a boiling range of 40—60° and the ligroin 90—100°.

4-Amino-1-phenylpyrazole.—4-Nitro-1-phenylpyrazole (20·0 g.) was refluxed with ethanol (100 c.c.), 60% hydrazine hydrate (40 c.c.), and 5% palladised charcoal (2·0 g.) for 10 min. The catalyst was filtered off, and the filtrate evaporated to small bulk, diluted with water, and set aside. Colourless needles of 4-amino-1-phenylpyrazole separated (14·3 g., 85%), m. p. 103—104°, raised to 104—105° on recrystallisation from ligroin.

1′-Phenylpyrazolo(4′ : 5′-2 : 3)pyridine.—Sulphuric acid (22·6 g.; *d* 1·84) was slowly added to a mixture of 4-amino-1-phenylpyrazole (17·2 g.), anhydrous glycerol (42·3 g.), nitrobenzene (8·9 g.), and ferrous sulphate (5·3 g.), and the mixture was heated at 180—185° for 4 hr. When cool, the mixture was diluted with water, filtered, and steam-distilled to remove excess of nitrobenzene. It was then made alkaline with 10% aqueous sodium hydroxide and again steam-distilled to remove quinoline. The distillation was continued until a portion of the filtrate no longer gave a precipitate of quinoline picrate when treated with an ethanolic solution of picric acid. The mixture was filtered and the tarry residue and the filtrate were separately extracted with benzene. The residue obtained after the removal of benzene was distilled *in vacuo*, to give material (5·5 g., 26·0%), b. p. 114—116°/0·1 mm., m. p. 58—62°, which was then chromatographed in benzene on alumina. Elution with benzene gave crystals which, on recrystallisation from light petroleum, gave *1′-phenylpyrazolo(4′ : 5′-2 : 3)pyridine* (4·0 g., 19%) as needles, m. p. 72—73° (Found: C, 73·6; H, 4·4; N, 21·5. $C_{12}H_9N_3$ requires C, 73·9; H, 4·6; N, 21·5%).

3-Methyl-1-p-nitrophenylpyrazole.—4 : 4-Dimethoxy-2-butanone [7] (50·0 g., 1 mol.) and *p*-nitrophenylhydrazine hydrochloride (71·8 g., 1 mol.) were refluxed in 50% ethanol (600 c.c.). After 10 min. the hot solution deposited reddish-brown needles which, recrystallised from ethanol, gave 3-methyl-1-*p*-nitrophenylpyrazole (49·0 g., 64·2%), m. p. 170—170·5° (Burness [8] gives 165·5°; Knorr [11] gives 165°).

3-Methyl-4-nitro-1-p-nitrophenylpyrazole.—A mixture of sulphuric acid (165 c.c.; *d* 1·84) and nitric acid (165 c.c.; *d* 1·42) was added dropwise with stirring during 1 hr. to a cooled solution of 3-methyl-1-*p*-nitrophenylpyrazole (25·0 g.) in sulphuric acid (200 c.c.; *d* 1·84). The solution was kept at 22° for 16 hr., then poured on ice. The yellow solid was washed and dried (29·0 g., 95·0%; m. p. 201—203°). A portion on recrystallisation from benzene gave *3-methyl-4-nitro-1-p-nitrophenylpyrazole* as pale yellow needles, m. p. 203—205° (Found: C, 48·1; H, 3·6; N, 22·8. $C_{10}H_8O_4N_4$ requires C, 48·4; H, 3·2; N, 22·6%).

1-p-Aminophenyl-3-methyl-4-nitropyrazole.—3-Methyl-4-nitro-1-*p*-nitrophenylpyrazole (30·0 g.) (m. p. 201—203°) was suspended in ethanol (800 c.c.) containing aqueous ammonia (120 c.c.; *d* 0·880). Hydrogen sulphide was passed in for 15 min., and the mixture was then refluxed for 30 min. and finally cooled. This process was repeated twice. When then set aside, the reaction mixture deposited lemon-yellow needles which were collected and extracted with boiling 0·75N-hydrochloric acid (900 c.c.). The hot extract, when made alkaline with aqueous ammonia (*d* 0·88), gave *1-p-aminophenyl-3-methyl-4-nitropyrazole*, lemon-yellow needles (from ethanol) (22·6 g., 86·5%), m. p. 167—168° (Found: C, 55·0; H, 4·7; N, 25·5. $C_{10}H_{10}O_2N_4$ requires C, 55·0; H, 4·6; N, 25·7%).

3-Methyl-4-nitro-1-phenylpyrazole.—1-*p*-Aminophenyl-3-methyl-4-nitropyrazole (18·2 g.) was dissolved in 70% w/w sulphuric acid (150 c.c.) and diazotised at 40° with sodium nitrite (6·65 g.; 10% excess) in sulphuric acid (20 c.c.; *d* 1·84). The solution was kept at 35—40° for 2 hr., then diluted with water (100 c.c.). The diazonium sulphate solution was added dropwise

[10] Das Gupta, *J. Indian Chem. Soc.*, 1952, **29**, 711.
[11] Knorr, *Annalen*, 1894, **279**, 221.

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during 1 hr. to a stirred solution of 31% w/w hypophosphorous acid (260 g.) at 20°. The solution was set aside overnight. The product, a yellow solid, was collected, washed, and dried (14·6 g., 87·5%; m. p. 107—109°). The crude deamination product was chromatographed in benzene on alumina which was then eluted with a 1% solution of methanol in benzene. The yellow solid obtained recrystallised from benzene–light petroleum, to give yellow needles of *3-methyl-4-nitro-1-phenylpyrazole*, m. p. 109—110·5° (Found: C, 58·8; H, 4·2; N, 20·45. $C_{10}H_9O_2N_3$ requires C, 59·1; H, 4·4; N, 20·7%).

4-Amino-3-methyl-1-phenylpyrazole.—A mixture of 3-methyl-4-nitro-1-phenylpyrazole (14·0 g.; m. p. 107—109°), 60% hydrazine hydrate (30 c.c.), 5% palladised charcoal (4·1 g.) and ethanol (400 c.c.) was heated on the steam-bath for 1 hr. Working up as in the preparation of 4-amino-1-phenylpyrazole gave a dark-red impure solid. This was extracted with boiling ligroin which, on cooling, deposited colourless needles of the amine (5·7 g., 48%), m. p. 88—89·5° (Michaelis and Schäfer [6] give 88°).

3'-Methyl-1'-phenylpyrazolo(4' : 5'-2 : 3)pyridine.—Sulphuric acid (7·4 g.; *d* 1·84) was slowly added to a stirred mixture of 4-amino-3-methyl-1-phenylpyrazole (6·1 g.), glycerol (13·9 g.), nitrobenzene (3·0 g.), and ferrous sulphate (2 g.). The mixture was heated at 180—185° for 4 hr. and worked up as in the preparation of 1'-phenylpyrazolo(4' : 5'-2 : 3)-pyridine. The benzene extract gave, on evaporation, a brown viscous tar. This was distilled under reduced pressure, to give a product (3·54 g., 48·5%), m. p. 59—63°, which was chromatographed in benzene on alumina. Elution with benzene gave a colourless solid, which, on recrystallisation from light petroleum gave *3'-methyl-1'-phenylpyrazolo(4' : 5'-2 : 3)pyridine*, m. p. 71·5—72·5° (Found: C, 74·5; H, 5·5; N, 19·8. $C_{13}H_{11}N_3$ requires C, 74·6; H, 5·3; N, 20·1%).

Ethyl 2 : 4-Dioxopentanoate.—This was prepared from acetone and ethyl oxalate in 71% yield (b. p. 110—112°/15 mm.) by the method of Marvel and Dreger [12] (these authors obtained 61—66% of ester, b. p. 132°/37 mm.).

Condensation between Ethyl 2 : 4-Dioxopentanoate and Phenylhydrazine.—Phenylhydrazine (119·0 g., 1 mol.) was added during 45 min. to a stirred solution of ethyl 2 : 4-dioxopentanoate (174·0 g., 1 mol.) in glacial acetic acid (400 c.c.). The solution was refluxed for 2 hr., then poured into water (1200 c.c.). The yellow oil which separated was extracted with ether (1 × 500 c.c.; 4 × 250 c.c.), and the combined extracts were washed with 10% sodium carbonate solution (4 × 200 c.c.), then with water (3 × 50 c.c.). The extracts were dried (Na_2SO_4) and on evaporation gave a yellow viscous oil which was distilled *in vacuo*. *Ethyl 3-methyl-1-phenylpyrazole-5-carboxylate* (51·6 g., 20·3%) had b. p. 106—108°/0·1 mm., m. p. 40—41° (Found: C, 68·1; H, 5·8; N, 11·9. $C_{13}H_{14}O_2N_2$ requires C, 67·8; H, 6·1; N, 12·2%). Ethyl 5-methyl-1-phenylpyrazole-3-carboxylate (153·85 g., 60·6%) had b. p. 128—130°/0·1 mm., m. p. 35—36°. (These two low-melting esters formed an oil when mixed at room temperature.)

Orientation of the Pyrazole Esters.—The higher-boiling ester (178·0 g.) was heated on the steam-bath with ethanol (300 c.c.), water (50 c.c.) and potassium hydroxide (69·5 g.) for 30 min. Most of the ethanol was removed under reduced pressure. Water (150 c.c.) was added and the solution acidified with hydrochloric acid (*d* 1·18). The pyrazole acid was collected and dried *in vacuo* ($CaCl_2$) to give 5-methyl-1-phenylpyrazole-3-carboxylic acid as the monohydrate (165 g., 97%), m. p. 103—104°. A portion on recrystallisation from aqueous ethanol had m. p. 106°. When kept *in vacuo* over calcium chloride for one week, the anhydrous acid was obtained, having m. p. 136°. The lower-boiling ester gave, on hydrolysis, colourless needles of 3-methyl-1-phenylpyrazole-5-carboxylic acid, m. p. 189—190° (from aqueous ethanol).

5-Methyl-1-phenylpyrazole.—5-Methyl-1-phenylpyrazole-3-carboxylic acid (163·0 g.), m. p. 103—104°, was decarboxylated at 200—210°. The residual dark brown liquid was distilled under reduced pressure to give 5-methyl-1-phenylpyrazole (93·0 g., 78·8%), b. p. 134—136°/13 mm.

5-Methyl-4-nitro-1-p-nitrophenylpyrazole.—5-Methyl-1-phenylpyrazole (70·0 g.) was nitrated with mixed acids as for the 3-methyl isomer. The crude product (108·7 g., 98·5%) was obtained as a pale yellow solid, m. p. 146—150°. Recrystallisation from benzene gave pale yellow needles of *5-methyl-4-nitro-1-p-nitrophenylpyrazole*, m. p. 155—157° (Found: C, 48·6; H, 3·1; N, 22·3. $C_{16}H_8O_4N_4$ requires C, 48·4; H, 3·2; N, 22·6%).

1-p-Aminophenyl-5-methyl-4-nitropyrazole.—5-Methyl-4-nitro-1-*p*-nitrophenylpyrazole

[12] Marvel and Dreger, *Org. Synth.*, Coll. Vol. III, 1955, p. 685.

(103·8 g.), m. p. 146—150°, was suspended in ethanol and reduced with ammonium hydrogen sulphide as for the 3-methyl isomer. Lemon-yellow 1-p-*aminophenyl-5-methyl-4-nitropyrazole* (60·7 g., 66·5%) had m. p. 146—148° (from aqueous ethanol) (Found: C, 55·3; H, 4·3; N, 25·3. $C_{10}H_{10}O_2N_4$ requires C, 55·0; H, 4·6; N, 25·7%).

5-Methyl-4-nitro-1-phenylpyrazole.—1-*p*-Aminophenyl-4-nitropyrazole (59·0 g.; m. p. 144—148°) was diazotised in 70% sulphuric acid with sodium nitrite (25·0 g., 10% excess) in sulphuric acid (50 c.c.; *d* 1·84) at 35—40°. After 2 hr. at this temperature the solution was cooled, filtered, and added dropwise during 1 hr. to stirred aqueous 31% w/w hypophosphorous acid (260 g.) at 20°. The solution was set aside overnight and the yellow solid was filtered off, washed, and dried (50·0 g., 90·9%). This (30·0 g.) was chromatographed in benzene on alumina. The yellow solid obtained on elution with a 1% solution of methanol in benzene recrystallised from benzene–light petroleum, to give *5-methyl-4-nitro-1-phenylpyrazole* (25·4 g., 77·1%) as yellow needles, m. p. 113—114° (Found: C, 59·4; H, 4·7; N, 20·35. $C_{10}H_9O_2N_3$ requires C, 59·1; H, 4·4; N, 20·7%).

4-Amino-5-methyl-1-phenylpyrazole.—5-Methyl-4-nitro-1-phenylpyrazole (23·0 g.) was refluxed in ethanol (250 c.c.) with 60% hydrazine hydrate (60 c.c.) and 5% palladised charcoal (6·8 g.) for 1 hr. The catalyst was removed and the filtrate evaporated to dryness. (The last traces of water were removed by azeotropic distillation with benzene.) The residual viscous yellow oil (19·1 g., 97·5%) solidified and was used without purification in the next stage. A portion, distilled *in vacuo*, had b. p. 114—116°/0·08 mm., m. p. 32—33° (Found: C, 69·2; H, 6·1; N, 24·5. $C_{10}H_{11}N_3$ requires C, 69·4; H, 6·35; N, 24·3%).

Skraup Reaction with 4-Amino-5-methyl-1-phenylpyrazole.—Sulphuric acid (18·4 g.; *d* 1·84) was slowly added to a mixture of 4-amino-5-methyl-1-phenylpyrazole (15·0 g.), anhydrous glycerol (32·4 g.), nitrobenzene (7·4 g.), and ferrous sulphate (5·0 g.), and the mixture was then heated at 180—185° for 4 hr. When cool, the mixture was diluted with water, filtered, and steam-distilled to remove excess of nitrobenzene. When the mixture was made alkaline with 30% aqueous sodium hydroxide, a tar separated. This was steam-distilled until no more quinoline (identified as the picrate) was obtained in the aqueous distillate. The mixture was filtered and the residue and the filtrate were separately extracted with benzene. The extracts on evaporation gave a tarry residue which on distillation *in vacuo* gave a pale-yellow oil (0·3 g.), b. p. 114—116°/0·08 mm. The infrared spectrum of the oil was identical with that of authentic 4-amino-5-methyl-1-phenylpyrazole. No other product was obtained when extractions were carried out with ether and chloroform.

6-(1-Pyrazolyl)quinoline.—60% Sulphuric acid (60 g.) was cautiously added to a mixture of 1-*p*-aminophenylpyrazole (10·0 g.), anhydrous glycerol (11·2 g.), and arsenic pentoxide (10·0 g.). The mixture was slowly heated to the b. p., then refluxed for 3 hr. When cool, the solution was diluted with water, filtered, and made alkaline with 30% aqueous sodium hydroxide. The brown tar that was precipitated was extracted with benzene (4 × 200 c.c.). The extracts were washed with water (3 × 50 c.c.), and the benzene was removed by distillation. The residual brown oil, which solidified, was extracted with boiling ligroin. The latter was filtered free from insoluble material and evaporated. The residue was chromatographed in benzene on alumina. The yellow solid obtained on elution with benzene recrystallised from ether, to give yellow crystals (3·0 g., 23·9%), m. p. 115—116°. Recrystallisation from ligroin gave pale-yellow needle clusters of *6-(1-pyrazolyl)quinoline*, m. p. 116—117° (Found: C, 73·8; H, 4·4; N, 21·7. $C_{12}H_9N_3$ requires C, 73·9; H, 4·6; N, 21·5%).

6-(4-Nitro-1-pyrazolyl)quinoline.—Sulphuric acid was slowly added to a mixture of 1-*p*-aminophenyl-4-nitropyrazole (5·0 g.), anhydrous glycerol (4·5 g.), and arsenic pentoxide (5·0 g.). The mixture was refluxed for 3 hr., and, when cool, diluted with water, filtered, and made alkaline with 30% aqueous sodium hydroxide. The brown tar that was precipitated was collected and extracted with ether. The extracts on evaporation gave a brownish-yellow solid which was chromatographed in benzene on alumina. Elution with benzene gave a yellow solid, m. p. 224—225°. Recrystallisation from benzene–light petroleum gave pale yellow needles of *6-(4-nitro-1-pyrazolyl)quinoline*, m. p. 225—226° (Found: C, 59·7; H, 3·3; N, 23·3. $C_{12}H_8O_2N_4$ requires C, 60·0; H, 3·3; N, 23·3%).

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668. *The* ^{18}O *Effect on the Infrared Absorption of Triphenylphosphine Oxide, and the Structure of Triphenylphosphine Oxide Hydrate.*

By M. Halmann and S. Pinchas.

The stretching vibration of the phosphoryl group in triphenylphosphine [^{18}O]oxide was compared with that of normal triphenylphosphine oxide. The frequency and intensity of the P–^{18}O band are appreciably lower than those of the P–^{16}O band. The results were used for determination of ^{18}O content in triphenylphosphine oxide. The absence of oxygen exchange between triphenylphosphine oxide and water indicates that triphenylphosphine oxide hydrate does not have the dihydroxy-structure.

In a study of the effect of ^{18}O on the infrared absorption of various compounds, the spectrum of triphenylphosphine [^{18}O]oxide was compared with that of the normal phosphine oxide.

The infrared spectra of a mineral oil mull and of a carbon disulphide solution of normal triphenylphosphine oxide have been reported.[1] For the mull there is a strong phosphoryl absorption band at 1190 cm.$^{-1}$, as well as a strong band at about 1125 cm.$^{-1}$ which was not assigned. For a carbon disulphide solution these bands appear at 1203 and 1121 cm.$^{-1}$, respectively. In the present work the absorption of the two triphenylphosphine oxides, containing 86 and 0·2 atom % of ^{18}O respectively, was measured for carbon tetrachloride solutions. The results are in agreement with those previously observed (Table 1). The

Table 1. *Major absorption bands of triphenylphosphine* [^{16}O]- *and* [^{18}O]-*oxide.*

Normal Ph_3PO [a]	3070	1438	1313	1202(s)	—	1123(s)	1070	752	746	694	690	683 cm.$^{-1}$
Labelled oxide [b]	3065	1438	1314	1205	1172(s)	1123(s)	1072	751	746	694	689	682 cm.$^{-1}$

[a] The bands down to 1070 cm.$^{-1}$ were measured with a 0·1 mm. cell filled with a 0·05 g./ml. solution in carbon tetrachloride; the lower bands with a Nujol mull. [b] The bands down to 1072 cm.$^{-1}$ refer to a 0·2 mm. cell and a 0·04 g./ml. carbon tetrachloride solution; the lower ones with a mull. s = A strong band.

spectrum is almost the same in the two cases. The strong band of the normal compound at 1202 ± 1 cm.$^{-1}$ is however much weaker in the spectrum of the phosphine oxide containing 86 atoms % ^{18}O. In the spectrum of the labelled compound an intense band appears at 1172 cm.$^{-1}$, where the normal oxide does not absorb significantly. It is thus evident that the band at 1202 cm.$^{-1}$ belongs to the P^+–$^{16}O^-$ stretching vibration.

The small decrease in the frequency (1190 cm.$^{-1}$) observed for the P^+–$^{16}O^-$ vibration in a mull of the oxide [1] must be attributed to the effect of intermolecular forces in the solid state. A mull of the labelled compound shows its P^+–$^{18}O^-$ absorption band at about 1152 cm.$^{-1}$.

The neighbouring absorption band at 1123 cm.$^{-1}$ occurs at the same frequency and with the same intensity in both the normal and the labelled triphenylphosphine oxide. There is thus no possibility that this band also belongs to a P–O stretching vibration of a rotational isomer.[2] It seems to be due to an in-plane (phenyl ring) C–H deformation vibration, by analogy with the 1157 cm.$^{-1}$ band of chlorobenzene.[3] The somewhat lower frequency in this case, which is also outside the region 1175—1125 cm.$^{-1}$ usually assigned to monosubstituted benzenes,[4] might be the result of weak interaction of the ring π-electrons with the positively charged phosphorus atom. This interaction would give rise to resonating contributing structures such as (I) which have a positive charge on *ortho*- or *para*-positions, thereby weakening their C–H bonds. The intensity of this band in this case, compared with the usual weakness of this band

(I)

[1] Daasch and Smith, *Analyt. Chem.*, 1951, **23**, 857; Geddes, *J. Phys. Chem.*, 1954, **58**, 1062.
[2] Mortimer, *Spectrochim. Acta*, 1957, **9**, 270.
[3] Hellwaege, "Landolt–Boernstein, Zahlenwerte und Funktionen," Springer Verlag, Berlin, VIth edn., Vol. I, Part 2, p. 304.
[4] Bellamy, "The Infrared Spectra of Complex Molecules," Methuen & Co., London, 1956, p. 55.

in other cases,[4] can also be explained by this interaction. This interaction cannot be assumed to be appreciable, however.[5],

The difference of 30 cm.$^{-1}$ between the stretching vibrations of P–^{16}O and P–^{18}O is similar to that observed [6] with the carbonyl vibrations of normal and labelled benzophenone (29 cm.$^{-1}$) and can be compared with the value of 45 cm.$^{-1}$ calculated for it according to Hooke's law when account is taken only of the phosphoryl group.

It has been observed [6] that when ^{18}O is introduced into benzophenone instead of ^{16}O the (apparent) molecular extinction coefficient of the RO band (R = P or C) drops from 360 to 300 l. mole^{-1} cm.$^{-1}$. When the corresponding molecular extinction coefficients of the triphenylphosphine oxides were calculated from the optical densities of their solutions in carbon disulphide at the R–O frequencies a similar drop from 425 to 360 l. mole^{-1} cm.$^{-1}$ was again observed. The half-intensity band width in both cases is equal and amounts to 13 cm.$^{-1}$, so that if a similar shape is assumed for the two bands the calculated absolute integrated intensities of these bands are in the same ratio as the corresponding molecular extinction coefficients. When the P$^+$–O$^-$ molecular extinction coefficients were measured in carbon tetrachloride solutions the values obtained were 410 and 310 l. mole^{-1} cm.$^{-1}$ and the half-widths 17 and 19 cm.$^{-1}$, respectively. If one takes the product of the extinction coefficient and the half-width as a measure of the corresponding integrated intensity of absorption,[7] one gets the results summarised in Table 2.

TABLE 2. *The relative absorption intensity* [a] *(l. mole^{-1} cm.$^{-1}$) of the phosphoryl stretching vibration.*

Vibration	In CCl_4	In CS_2
P$^+$–^{16}O$^-$	7000	5500
P$^+$–^{18}O$^-$	5900	4700

[a] Expressed as the product of the apparent molecular extinction coefficient and the half-intensity band width.

Table 2 shows that the absorption intensity of the P$^+$–^{18}O$^-$ band is always lower by about 15% than that of the corresponding P$^+$–^{16}O$^-$ band. This lower intensity of the absorption of the heavier isotopic group is larger than that calculated according to Crawford's rule.[8] As shown above the only frequency really affected by the ^{18}O replacement of ^{16}O in this case is the P–O frequency. One can therefore assume the intensities of all the other bands to be the same in the isotopic pair, as was found experimentally for the 1123 cm.$^{-1}$ band (see p. 3266). Crawford's rule therefore reduces here to the form: [9] $I_{16}/\nu_{16}^2 = I_{18}/\nu_{18}^2$ where I is the integrated intensity of the P–O band and ν is the P–O frequency. Hence, according to Crawford's rule the ratio I_{18}/I_{16} should be here $\nu_{18}^2/\nu_{16}^2 = 1172^2/1202^2 = 0{\cdot}95$, instead of the observed value of $0{\cdot}85 \pm 0{\cdot}05$.

The absolute absorption intensity of a vibration band is a function of the change of dipole moment of the vibrating molecule with the change in its normal co-ordinates during this vibration.[10] It seems therefore that the degree of polarisation of the P=O bond to P$^+$–O$^-$ is not the same in the two isotopic groups resulting in a bigger free charge e on the ^{16}O atom. This will give a larger bond moment $M = er$ (where r is approximately equal to the P–O bond length), and a higher molecular dipole moment. The change of the unequal molecular dipole moments of the normal and the labelled triphenylphosphine oxide with the change of the normal co-ordinates during a P$^+$–O$^-$ stretching vibration would probably also be unequal, resulting in different values for the relative absorption intensity of the P–O band.

A similar effect was observed by Nolin and Jones,[11] who found that the absorption

[5] Yaffe and Freeman, *J. Amer. Chem. Soc.*, 1952, **74**, 1069; *J. Chem. Phys.*, 1954, **22**, 1430.
[6] Halmann and Pinchas, *J.*, 1958, 1703.
[7] Ramsay, *J. Amer. Chem. Soc.*, 1952, **74**, 72.
[8] Crawford, *J. Chem. Phys.*, 1952, **20**, 977.
[9] See, *e.g.*, Eggers, Hisatsune, and Van Alten, *J. Phys. Chem.*, 1955, **52**, 1124.
[10] Herzberg, "Infrared and Raman Spectra," Van Nostrand Co., New York, 1945, pp. 260—261.
[11] Nolin and Jones, *J. Amer. Chem. Soc.*, 1953, **75**, 5626.

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of the CD_3 and CD_2 groups in deuterated ketones is much weaker than that of the corresponding CH_3 and CH_2 groups.

The higher values for the absorption intensity obtained for the solutions in carbon tetrachloride than for carbon disulphide solutions are worthy of note. It was found that when no solvent–solute interaction takes place the integrated absorption of a band measured in carbon disulphide solution is about 1·1 times that measured in carbon tetrachloride. This is due to the difference in the electric polarisability of the solvents.[12] It may therefore be concluded that the triphenylphosphine oxide forms association complexes with the carbon tetrachloride molecules, in which the polarisation of the $P^+–O^-$ bond is increased by some kind of interaction. This conclusion would also explain why the $P^+–O^-$ band is broader in carbon tetrachloride solutions than in solutions in carbon disulphide, since the intermolecular forces inside the complex present in carbon tetrachloride solution can be expected to modify the " pure " $P^+–O^-$ frequency somewhat differently for different configurations of this complex. A host of $P^+–O^-$ bands will thus be formed, all merging together to one broad band. This effect will then be somewhat similar to that of hydrogen bonding which also both increases the integrated absorption intensity of bands and broadens them.[13]

The benzophenone C=O band, measured for a carbon disulphide solution, has a half-intensity width not much different from that for a carbon tetrachloride solution (18 and 19 $cm.^{-1}$ respectively). The difference in the relative absorption intensity of the C=O band in these solvents is also smaller in this case, being only about 14% higher in carbon tetrachloride than in carbon disulphide, compared with 27% for the normal triphenylphosphine oxide. The width of the C=O band in solutions of normal and labelled benzophenone in carbon tetrachloride is practically the same. It can thus be assumed that the carbon tetrachloride–[^{16}O or ^{18}O]benzophenone interaction is only weak.

The relative absorption intensity of the 1123 $cm.^{-1}$ band was found to be constant within the experimental error when ^{16}O was replaced by ^{18}O in triphenylphosphine oxide, its value being always 4000 ± 200 l. $mole^{-1}$ $cm.^{-2}$.

It seems that this effect of the ^{18}O isotope on the intensity of the R=O band should be taken into account when the additivity of the bond moments in carbon dioxide is investigated by measuring the intensity of the $^{16}O=C=^{18}O$ absorption.[14]

The characteristic P–^{18}O infrared absorption of triphenylphosphine oxide was used in a tracer study for the elucidation of the structure of triphenylphosphine oxide hydrate which has been in some doubt. It is prepared by hydrolysis of triphenylphosphine dihalides [15] or by recrystallising the phosphine oxide from water.[16] Our analytical results fit best a hemihydrate formula $(Ph_3PO)_2,H_2O$, whereas previous authors [15,16] suggested a monohydrate formula Ph_3PO,H_2O. Jensen concluded from the considerable dipole moment of triphenylphosphine oxide that the phosphoryl bond is semipolar.[16] The dipole moment of triphenylphosphine oxide hydrate is even larger and therefore the water molecule could be expected to be bound by a hydrogen bridge to the oxygen atom of the phosphoryl group. The increased dipole moment in the hydrate was also explained by formation of a phosphonium hydroxide: [16] $Ph_3P^+–O^- \cdots H–OH \rightleftharpoons Ph_3P^+OH\ OH^-$. An altogether different structure might, however, be proposed on the basis of the short length of the P–O bond in the oxide,[17] which was assumed therefore to be a double bond. The hydrate could then be formed by addition of water to the double bond: $Ph_3PO + H_2O \rightleftharpoons Ph_3P(OH)_2$. In this dihydroxy-structure the two oxygen atoms become equivalent. To decide this, triphenylphosphine oxide was refluxed with an excess of water containing 87 atoms % of ^{18}O for 16 hr.; the phosphine oxide was then recovered

[12] Yaffe and Kimel, *J. Chem. Phys.*, 1956, **25**, 374.
[13] See, *e.g.*, Wenograd and Spurr, *J. Amer. Chem. Soc.*, 1957, **79**, 5844.
[14] Eggers and Arends, *J. Chem. Phys.*, 1957, **27**, 1405.
[15] Michaelis and Gleichman, *Ber.*, 1882, **15**, 801; Michaelis and Soden, *Annalen*, 1885, **229**, 306.
[16] Jensen, *Z. anorg. Chem.*, 1943, **250**, 270.
[17] Phillips, Hunter, and Sutton, *J.*, 1945, 146.

by drying the reaction mixture in a high vacuum. It did not become enriched in ^{18}O, within experimental error. Also, triphenylphosphine [^{18}O]oxide was boiled and recrystallised from normal water: its ^{18}O content did not decrease appreciably. The absence of oxygen exchange between triphenylphosphine oxide and water indicates that in the hydrate the oxygen atoms are not identical; the dihydroxy-structure can therefore be excluded.

The infrared spectrum of the normal hydrate also shows that it does not have the dihydroxy-structure. Its solution (0·05 g./l.) in carbon tetrachloride in a 0·02 mm. cell showed bands at 3410 (bonded OH stretching), 3070, 1483, 1438, 1311, 1201 (vs), 1119 (s), 1072, 1029, 1000. Comparison with Table 1 shows that the bands of the oxide are almost unaffected by the added water molecule, the presence of the latter in the solution being clearly demonstrated by the band at 3410 cm.$^{-1}$. It must be concluded that the hydrate is a molecular complex between the phosphine oxide and the water molecule. This complex would seem to be held together more by interactions between the aromatic rings and the water molecule than by hydrogen bonding to the phosphoryl group. This seems to be indicated by the lack of decrease in the $P^+–O^-$ frequency in the hydrate and, on the other hand, the decrease of 4 cm.$^{-1}$ in the C–H bending frequency.

Experimental

A solution of bromine (0·2 ml.; vacuum-distilled from P_2O_5) in dry carbon tetrachloride (5 ml.) was slowly added to a stirred solution of triphenylphosphine (0·80 g.; Eastman Organic Chemicals) with exclusion of moisture ($CaCl_2$). Triphenylphosphine dibromide was precipitated and the solution became brown owing to excess of bromine. After 10 minutes' stirring, water containing 87 atoms % of ^{18}O (0·5 ml., from the fractionating plant of this Institute) was added at once by means of a syringe, and the mixture was refluxed for ½ hr. with stirring. The carbon tetrachloride and most of the excess of water were then distilled off. The residual viscous mass crystallised from a large volume of normal distilled water; crystals of triphenylphosphine [^{18}O]oxide were obtained (0·27 g.) which, dried in a vacuum, had m. p. 158·5—159·5° (lit.,[17] m. p. 159°).

Triphenylphosphine oxide hydrate, prepared according to Michaelis's procedure,[15] was recrystallised from water; it had m. p. 154—157° (Michaelis [15] reports 148°) [Found: C, 75·25; H, 5·6; H_2O, 3·6 (Karl Fischer). Calc. for the hemihydrate $C_{36}H_{32}O_3P_2$: C, 75·3; H, 5·6; H_2O, 3·1%). The average of Jensen's cryoscopic molecular-weight determinations [16] in benzene is 287 (calc. for hemihydrate: 287; for monohydrate, 296; on the assumption that in the benzene solution the water molecule remains attached to one triphenylphosphine oxide molecule).

The infrared light absorption was measured with a Perkin–Elmer infrared spectrophotometer Model 12C equipped with a sodium chloride prism. The molecular extinction coefficients of the isotopic pairs were determined in the same cell and usually on more than one solution. The thickness of the cells is, however, known only to the first decimal figure, hence the relative values for the molecular extinction coefficient are estimated to be correct to within 10 l. mole^{-1} cm.$^{-1}$, but the "absolute" (apparent) values are much less exact. The relative intensity values are estimated to be correct to about 200 units. The slit width used at 1100—1300 cm.$^{-1}$ was about 0·15 mm.

Determination of the ^{18}O content in triphenylphosphine oxide was at first attempted by the method of Rittenberg and Ponticorvo.[18] It was found, however, that a mixture of mercuric chloride and the phosphine oxide at 425° did not liberate carbon dioxide. Triphenylphosphine oxide was decomposed by heating it (about 15 mg.) with mercuric chloride (about 15 mg.) and mercuric cyanide [19] (about 25 mg.) in an evacuated break-seal tube. The remaining procedure was as described in the literature.[18]

We thank Mr. S. Kimel of this Institute for valuable discussions.

The Weizmann Institute of Science,
Rehovoth, Israel.

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[18] Rittenberg and Ponticorvo, *J. Appl. Rad. Isot.*, 1956, **1**, 208.
[19] We are indebted to Dr. M. Anbar for suggesting the use of mercuric cyanide.

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669. *Studies of Trifluoroacetic Acid. Part XV.* Further Investigations on the Reactions of Acyl Trifluoroacetates with Hydroxy-compounds.*

By E. J. Bourne, M. Stacey, J. C. Tatlow, and R. Worrall.

Acyl trifluoroacetates with hydroxy-compounds give the trifluoroacetyl and other acyl esters, in proportions depending on the nature of the anhydride and hydroxy-compound; in most cases the "other acyl" ester predominates. The yields of acyl esters relative to trifluoroacetyl esters are usually increased by the presence of trifluoroacetic acid, and decreased by that of sodium trifluoroacetate and by solvents of low ionising ability. The manner in which the structure of a hydroxy-compound influences the course of its reactions with acyl trifluoroacetates is discussed. Alcohols capable of giving a stabilised carbonium ion react with acyl trifluoroacetate–trifluoroacetic acid mixtures by alkyl–oxygen fission.

It is well established that trifluoroacetic anhydride promotes acylations (as used in this paper the term excludes trifluoroacetylation) of hydroxy-compounds [1] and of compounds possessing reactive aromatic nuclei [2] by many carboxylic acids. These reactions proceed [3] *via* unsymmetrical anhydrides (acyl trifluoroacetates) formed from the acid and the trifluoroacetic anhydride. It has been suggested further,[4,5] and supporting evidence based on conductivities has been adduced,[6] that these unsymmetrical anhydrides ionise to a limited extent into acylium ($R{\cdot}CO^+$) and trifluoroacetate ($CF_3{\cdot}CO_2^-$) ions, the former ions or solvated forms being the principal acylating species. The acylating, as opposed to trifluoroacetylating, power of acyl trifluoroacetates was considerably enhanced [3] by the

$$R{\cdot}CO_2H + (CF_3{\cdot}CO)_2O \rightleftharpoons R{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CF_3 + CF_3{\cdot}CO_2H \quad . \quad . \quad . \quad . \quad . \quad . \quad (I)$$

trifluoroacetic acid liberated as they were formed in the above mixtures [equilibrium (I)]. With the unsymmetrical anhydrides in the absence of added acid, trifluoroacetylation became a more important process,[3] particularly in reactions with lower aliphatic alcohols and aromatic amines. This paper extends the investigations [3] of the reactions of acyl trifluoroacetates to cover different types of hydroxy-compounds and of acyl trifluoroacetates, and shows the broad effects on the process of the structures of the reactants.

Results

Methods Used.—For the comprehensive studies envisaged, a new and simple method for the analysis of acyl and trifluoroacetyl ester products was required. Acyl trifluoroacetates derived from acetic, benzoic, and phenylacetic acid were available,[3] and it was shown that, in their infrared spectra, the carbonyl stretching frequencies for the esters of these acids in the range 1700—1800 cm.$^{-1}$ differed from those of the analogous trifluoroacetates by 25—65 cm.$^{-1}$, and this allowed an easy interpretation of their combined absorption spectra (see Table 6). The method required the preparation of each ester as a reference compound but was otherwise far superior to the anilide separation used before.[3]

Acetyl Trifluoroacetate Systems.—The reactions of acetyl trifluoroacetate, alone and in the presence of certain addenda, with a representative series of hydroxy-compounds were investigated, using the infrared method to provide a quantitative analysis of the products

* Part XIV, *J.*, 1958, 1274.

[1] Bourne, Stacey, Tatlow, and Tedder, *J.*, 1949, 2976.
[2] *Idem*, *J.*, 1951, 718.
[3] Bourne, Stacey, Tatlow, and Worrall, *J.*, 1954, 2006.
[4] Bourne, Randles, Tatlow, and Tedder, *Nature*, 1951, **168**, 942.
[5] Bourne, Randles, Stacey, Tatlow, and Tedder, *J. Amer. Chem. Soc.*, 1954, **76**, 3206.
[6] Randles, Tatlow, and Tedder, *J.*, 1954, 436.

obtained. The results of these reactions are given in Table 1. The conditions used before [3] for the reactions of *n*-, *sec.*-, and *tert.*-butyl alcohol with acetyl trifluoroacetate in ether are roughly comparable with those of columns III and IV of Table 1. The hydroxy-compounds now investigated may be divided into two broad groups, both of which can be

TABLE 1. *Esters formed in reactions of acetyl trifluoroacetate* (1·3 *mol.*) *with hydroxy-compounds* (ca. 0·0025 *mole*).

(For 2 hr. at 20° unless otherwise stated.)

	I		II		III		IV	
Addenda:	—		$CF_3 \cdot CO_2H$ (1·3 mol.)		CCl_4 (0·5 c.c.)		$CF_3 \cdot CO_2H$ (1·3 mol.) CCl_4 (0·5 c.c.)	
R in ROH	ROAc (%)	RO·CO·CF_3 (%)	ROAc (%)	RO·CO·CF_3 (%)	ROAc (%)	RO·CO·CF_3 (%)	ROAc (%)	RO·CO·CF_3 (%)
Group 1a								
Bu^n	58	37	79	18	21	78	67	33
Et	73	25	87	12	29	66	76	22
Ph·CH_2	72	28	81	18	46	52	81	15
Bu^s	78	20	89	8	56	40	87	11
$[CH_2]_5 \rangle CH$	86	14	91	8	68	32	92	7
p-$NO_2 \cdot C_6H_4 \cdot CH_2$	93	4	96	4	86	14	86	14
Group 1b								
$CF_3 \cdot CMe_2$	96	—	99	—	95	—	99	—
$CF_3 \cdot CHMe$	96	—	96	—	96	—	96	—
$CF_3 \cdot CH_2$	100	—	100	—	98	—	96	—
Ph	98	—	96	—	98	—	95	—
Group 2a								
Bu^t	55	41	4	90	96	3	36	64
Ph·CHMe	61	39	4	94	74	24	4	94
Group 2b								
Ph_2CH	Polymers		Polymers		29	68	11	89
p-MeO·C_6H_4·CHPh	Polymers		Polymers		12	87	Polymers	

	V		VI		VII	
Addenda:	CCl_4 (25 c.c.)		$CF_3 \cdot CO_2H$ (1·3 mol.) CCl_4 (25 c.c.)		$CF_3 \cdot CO_2Na$ (1·5 mol.)	
R in ROH	ROAc (%)	RO·CO·CF_3 (%)	ROAc (%)	RO·CO·CF_3 (%)	ROAc (%)	RO·CO·CF_3 (%)
Group 1a						
Bu^n	6 *	90 *	9 *	90 *	15	79
Ph·CH_2	18 *	81 *	28 *	71 *		
Bu^s	30 *	67 *	30 *	68 *	20	74
$[CH_2]_5 \rangle CH$	35 *	64 *	33 *	67 *	—	—
p-$NO_2 \cdot C_6H_4 \cdot CH_2$					33	66
Group 1b						
$CF_3 \cdot CMe_2$	21 *	—	67 *	—		
$CF_3 \cdot CHMe$	50 *	—	79 *	—		
$CF_3 \cdot CH_2$	91 *	—	98 *	—	36	61
Ph	90 *	—	96 *	—	44	50
Group 2a						
Bu^t	50 *	4 *	70 *	4 *	84	15
Ph·CHMe	42	54	67	30	35	64
Group 2b						
Ph_2CH	74	26	39	57		
p-MeO·C_6H_4·CHPh	16	84	6	87		

* Reaction for 1 hr.

further subdivided making four sub-groups, 1a, 1b, 2a, 2b, each with a distinctive mode of reaction.

Trifluoroacetic acid clearly plays an important rôle in esterifications with acetyl trifluoroacetate. It should be noted that it is liberated when the anhydride reacts with

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a hydroxy-compound to give an acetate [equation (2)], whilst if a trifluoroacetate is produced acetic acid is formed [equation (3)]. Acetic acid can itself react with acetyl trifluoroacetate with the formation [7] of acetic anhydride and trifluoroacetic acid [equilibrium (4)].

Obviously, therefore, the reactions of acetyl trifluoroacetate with hydroxy-compounds will always be complicated by these effects, and those in which no reactive addenda were included (Table 1, columns I, III, and V) are really composite reactions in which, in the later stages, the effects of the liberated acids may be quite pronounced.

$$X{\cdot}OH + CH_3{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CF_3 \longrightarrow X{\cdot}O{\cdot}CO{\cdot}CH_3 + CF_3{\cdot}CO_2H \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$X{\cdot}OH + CH_3{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CF_3 \longrightarrow X{\cdot}O{\cdot}CO{\cdot}CF_3 + CH_3{\cdot}CO_2H \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$CH_3{\cdot}CO_2H + CH_3{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CF_3 \rightleftharpoons (CH_3{\cdot}CO)_2O + CF_3{\cdot}CO_2H \quad . \quad . \quad . \quad . \quad (4)$$

Sub-group 1*a*. With acetyl trifluoroacetate alone, the compounds of group 1a, the simple primary and secondary alcohols, gave mainly acetate esters, but these were accompanied by appreciable amounts of trifluoroacetates (Table I, column 1). The effect of the addition of trifluoroacetic acid is noteworthy (column II); it increased the acetate formed at the expense of the trifluoroacetate. Reaction of the hydroxy-compounds of sub-group 1a with acetyl trifluoroacetate and with acetyl trifluoroacetate–trifluoroacetic acid, under normal conditions with no diluent, is very rapid, and rates could only be determined after considerable dilution of the reactants with carbon tetrachloride. Samples of reaction mixtures (0·1M with respect to hydroxy-compound) were withdrawn at intervals and analysed for ester content. This dilution with carbon tetrachloride had a marked effect on the products [columns (V) and (VI) of Table 1] obtained with the alcohols of group 1a, and trifluoroacetylation became the main reaction. Trifluoroacetic acid had no appreciable effect on either the rates or the products of these reactions at high dilution. The primary alcohols reacted more rapidly and gave less acetate ester than the secondary alcohols. Since trifluoroacetylation was predominant, the rates of reaction of *n*- and *sec.*-butyl alcohol with trifluoroacetic acid, which could have been responsible for this type of acylation, were studied under the same conditions. Trifluoroacetylation did in fact occur but very much more slowly; again the primary reacted more rapidly than the secondary alcohol. The considerable influence exercised on the reactions of acetyl trifluoroacetate by a non-ionising solvent such as carbon tetrachloride, even in fairly small amounts, is shown in columns III and IV of Table 1. The proportions of trifluoroacetate formed were increased. The addition of sodium trifluoroacetate to acetyl trifluoroacetate also enhanced the formation of trifluoroacetate esters (column VII).

Sub-group 1*b*. The hydroxy-compounds of group 1b, phenol and fluoro-alcohols, reacted much more slowly with acetyl trifluoroacetate and gave exclusively acetate esters; however, with this group the rates of acetylation were increased greatly on addition of trifluoroacetic acid, even in high dilution with carbon tetrachloride. Differences in rates of reaction were also observed between the members of this sub-group. 2 : 2 : 2-Trifluoroethanol reacted more rapidly than 1-trifluoromethylethanol, and this more rapidly than 2 : 2 : 2-trifluoro-1 : 1-dimethylethanol. Dilution with carbon tetrachloride did not give rise to any trifluoroacetate, but addition of sodium trifluoroacetate did give over 50% of trifluoroacetate from phenol and from trifluoroethanol.

Group 2. Alcohols of group 2 gave quite different results. Diphenylmethanol and its 4-methoxy-derivative (group 2b) gave polymeric products when no inert diluent was used; in the presence of carbon tetrachloride, the addition of trifluoroacetic acid increased the yields of trifluoroacetate esters. With *tert.*-butyl alcohol and 1-phenylethanol (group 2a), the same effect applied in reactions involving trifluoroacetic acid with no diluent (columns I and II) or with little diluent (columns III and IV), and, contrary to the cases in group 1a, the addition of carbon tetrachloride increased the yields of acetate esters relative to those

[7] Bourne, Tatlow, and Worrall, *J.*, 1957, 315.

obtained from the neat mixtures. At much lower concentrations in carbon tetrachloride, however (columns V and VI), the effect of trifluoroacetic acid was to increase the proportion of acetate esters (general behaviour similar to that shown by members of group 1). Also, in the case of *tert.*-butyl alcohol, the rate of reaction under these conditions was increased by trifluoroacetic acid, as for group 1b. With *tert.*-butyl alcohol, the addition of sodium trifluoroacetate to acetyl trifluoroacetate considerably enhanced the production of acetate ester relative to reactions with no addenda or with added trifluoroacetic acid.

L-1-*Phenylethanol and Acetyl Trifluoroacetate Systems.*—Except for the reactions with group 2a at high dilution, the behaviour of the members of group 2 was clearly anomalous, and processes involving alkyl–oxygen fission at some stage were obviously indicated. The behaviour of L-1-phenylethanol and its esters with various reaction mixtures was therefore studied. A chromatographic separation of the acetate and trifluoroacetate of this alcohol was developed, which enabled this to be done. The results are given in Table 2.

With acetyl trifluoroacetate–trifluoroacetic acid under mild conditions, the L-alcohol gave extensively racemised trifluoroacetate (76%) together with inactive acetate (24%) showing that alkyl–oxygen fission had indeed occurred at some stage. The system was complex, however, since, while acetic acid or acetic anhydride did not appear to have any effect on the esters, trifluoroacetic acid alone readily racemised both the L-acetate and L-trifluoroacetate and converted much of the former into the trifluoroacetate. The presence of carbon tetrachloride inhibited both the interconversion and the racemisation. Trifluoroacetic acid and the L-alcohol gave the racemic trifluoroacetate. Acetyl trifluoroacetate alone had no effect on the L-acetate or the L-trifluoroacetate, but with the L-alcohol it gave partly racemised esters. The addition of progressively greater amounts of carbon tetrachloride to the last system first decreased and then increased the proportion of trifluoroacetate ester obtained; no racemisation occurred under these conditions. In the absence of diluent however, acetyl trifluoroacetate–trifluoroacetic acid gave much more extensive racemisation than when no acid was added. Acetyl trifluoroacetate–sodium trifluoroacetate and the L-alcohol afforded acetate ester (35%) and trifluoroacetate (64%), both however with complete retention of optical activity. These results show clearly that trifluoroacetic acid causes racemisation, presumably by protonation, but suggest that acetyl trifluoroacetate alone does not.

Acetyl Trifluoroacetate–Heptafluorobutyric Acid.—A brief study was made next of the system acetyl trifluoroacetate–heptafluorobutyric acid to confirm the probability that there was ready interchange between the acid and the anhydride in mixtures of this type. First, the system acetic anhydride–heptafluorobutyric anhydride was examined by infrared spectroscopy and it was established that the equilibrium favoured the unsymmetrical anhydride [equation (5)] as in the analogous case with trifluoroacetic

$$Ac_2O + (C_3F_7{\cdot}CO)_2O \rightleftharpoons 2Ac{\cdot}O{\cdot}CO{\cdot}C_3F_7 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

$$Ac{\cdot}O{\cdot}CO{\cdot}CF_3 + C_3F_7{\cdot}CO_2H \rightleftharpoons Ac{\cdot}O{\cdot}CO{\cdot}C_3F_7 + CF_3{\cdot}CO_2H \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

anhydride.[3] Infrared spectroscopic analysis of mixtures showed that equilibrium (6) was indeed established and that the equilibrium constant was very approximately 1. In its reaction with phenetole, acetyl trifluoroacetate–heptafluorobutyric acid gave a good yield (78%) of ketone in only 3 hr.; this acid thus had an effect comparable with that of trifluoroacetic acid [3] on the acylating power of the anhydride.

Benzoyl and Phenylacetyl Trifluoroacetate.—Benzoyl trifluoroacetate was found previously [3] to effect trifluoroacetylation much more readily than did acetyl trifluoroacetate. Infrared spectroscopy of esters has now been applied to the reactions of other hydroxy-compounds with benzoyl trifluoroacetate, alone and in the presence of certain addenda (Table 3). The series cannot be divided into clear-cut groups as before, but the hydroxy-compounds are arranged roughly in order of increasing yield of benzoate esters with benzoyl trifluoroacetate alone (column I). With the alcohols at the beginning of the series, trifluoroacetylation was the predominant reaction, but phenol at the end of the

series gave a good yield (75%) of the benzoate (column I). Addition of trifluoroacetic acid did not appreciably affect yields of benzoate esters with the alcohols in the series up to *p*-nitrobenzyl alcohol, but with this and the remainder of the hydroxy-compounds it caused a substantial increase in benzoate production (column II). When treated with

TABLE 2. *Reactions of* L-1-*phenylethanol and its esters.*

	Reactants (g.)					
	L-PhMeCH·O·R					
Expt. No.	R = H	R = Ac	R = CO·CF_3	CF_3·CO_2H	CF_3·CO_2Ac	CCl_4
1	—	0·64	—	0·90	—	—
2	—	0·28	—	0·39	—	16
3	—	0·31	—	—	0·36	—
4	—	0·72	—	0·66	0·97	—
5	—	0·21	—	0·19	0·26	16
6	—	—	0·30	0·31	—	—
7	—	—	0·19	0·20	—	1·6
8	—	—	0·18	0·20	—	16
9	—	—	0·27	—	0·26	—
10	—	—	0·27	0·33	0·46	—
11	—	—	0·18	0·13	0·17	16
12	1·22	—	—	2·28	—	—
13	1·08	—	—	—	1·81	—
14	1·20	—	—	1·48	2·05	—
15	1·36	—	—	—	2·28	8
16	1·22	—	—	—	2·04	300
17	0·39	—	—	0·20 *	0·65	—

		Esters formed							
		L-PhMeCH·O·CO·R′		Properties of product isolated			Properties of alcohol obtained by hydrolysis		
Expt. No.	Reaction time (hr.) at 20°	R′	Yield (% by infrared)	Yield (%)	B. p./ 15 mm.	Optical activity (%age retained)	Yield (%)	B. p./ 15 mm.	Optical activity (%age retained)
1	2	Me	28	24	96°	6	81	93°	6
		CF_3	69	48	74	0	78	94	0
2	2	Me	—	78	95	100	—	—	—
3	2	Me	—	82	96	100	—	—	—
4	2	Me	24	24	95	0	—	—	—
		CF_3	76	37	74	0	77	94	0
5	2	Me	—	89	95	100	—	—	—
6	2	CF_3	—	84	72	0	—	—	—
7	2	CF_3	—	66	72	83	—	—	—
8	2	CF_3	—	69	70	100	—	—	—
9	2	CF_3	—	76	72	100	—	—	—
10	4·5	CF_3	100	72	70	5	—	—	—
11	2	CF_3	—	72	70	100	—	—	—
12	4	CF_3	—	70	72	0	81	94	0
13	2	Me	61	45	94	42	85	93	42
		CF_3	39	23	75	12	57	93	12
14	0·5	Me	24	14	95	0	—	—	—
		CF_3	76	50	76	10	75	93	11
15	1	Me	76	61	94	100	—	—	—
		CF_3	21	13	73	100	81	93	100
16	4	Me	46	43	94	100	75	94	100
		CF_3	52	24	74	100	74	93	100
17	2	Me	35	24	93	100	—	—	—
		CF_3	64	26	70	100	—	—	—

* CF_3·CO_2Na.

benzoyl trifluoroacetate in carbon tetrachloride (columns IV and V) all the alcohols in the series up to and including *p*-nitrobenzyl alcohol gave exclusively trifluoroacetate esters even when the reactions were carried out in the presence of trifluoroacetic acid. Of the remaining hydroxy-compounds, with the unsymmetric anhydride alone in carbon

tetrachloride (column IV), only phenol gave a reasonable yield (76%) of benzoate ester, but the yields from the fluoro-alcohols were greatly increased on addition of trifluoroacetic acid (column V). When the reactions of *n*- and *sec.*-butyl and of *p*-nitrobenzyl alcohol with benzoyl trifluoroacetate were carried out in the presence of a large excess (10 mol.) of trifluoroacetic acid (column III) the proportions of benzoate esters were greatly increased and even the butyl alcohols gave reasonable yields (38 and 57% respectively).

TABLE 3. *Reactions of benzoyl trifluoroacetate* (1·3 *mol.*) *with hydroxy-compounds* (2 *hr. at* ca. 20°).

	I		II		III	
Addenda:	—		$CF_3 \cdot CO_2H$ (1·3 mol.)		$CF_3 \cdot CO_2H$ (10 mol.)	
R in ROH	ROBz (%)	RO·CO·CF_3 (%)	ROBz (%)	RO·CO·CF_3 (%)	ROBz (%)	RO·CO·CF_3 (%)
Bu^n	6	93	8	92	38	59
$Ph \cdot CH_2$	3	94	4	93		
Bu^s	5	92	8	92	57	40
$[CH_2]_5 \rangle CH$	5	94	9	90		
Et	12	84	13	81		
Bu^t	13	74	23	73	—	83
$p\text{-}NO_2 \cdot C_6H_4 \cdot CH_2$ *	16	83	64	35	92	8
$CF_3 \cdot CMe_2$	29	15	82	16		
$CF_3 \cdot CHMe$	18	57	94	6		
$CF_3 \cdot CH_2$	44	53	82	17		
Ph *	75	25	88	11		

	IV		V	
			$CF_3 \cdot CO_2H$ (1·3 mol.)	
Addenda:	CCl_4 (0·5 c.c.)		CCl_4 (0·5 c.c.)	
R in ROH	ROBz (%)	RO·CO·CF_3 (%)	ROBz (%)	RO·CO·CF_3 (%)
Bu^n	—	97	—	99
$Ph \cdot CH_2$	—	99	—	99
Bu^s	—	95	—	99
$[CH_2]_5 \rangle CH$	—	96	—	99
Et	—	96	—	97
Bu^t	—	86 *	—	87 *
$p\text{-}NO_2 \cdot C_6H_4 \cdot CH_2$ *	—	99	—	99
$CF_3 \cdot CMe_2$	21	13	50	25
$CF_3 \cdot CHMe$	11	51	85	15
$CF_3 \cdot CH_2$	20	67	80	19
Ph *	76	19	93	7

* Reaction for 2 hr. at *ca.* 50°.

The rates of reaction of butan-1-ol and of phenol with benzoyl trifluoroacetate, alone and in the presence of trifluoroacetic acid, in excess of carbon tetrachloride, showed that even phenol now gave mainly the trifluoroacetate. The reactions with butan-1-ol were as rapid as for acetyl trifluoroacetate. In the early stages of the reaction of benzoyl trifluoroacetate alone with phenol the same is true, but the main effect of trifluoroacetic acid here was to slow down considerably the formation of phenyl trifluoroacetate; the formation of phenyl benzoate was also enhanced somewhat.

Phenylacetyl trifluoroacetate seems to occupy an intermediate position as regards acylating power. The reactions of some hydroxy-compounds with phenylacetyl trifluoroacetate and phenylacetyl trifluoroacetate–trifluoroacetic acid were examined by infrared spectroscopy (Table 4), the hydroxy-compounds with the exception of *tert.*-butyl alcohol being listed in order of increasing yields of phenylacetate esters. The alcohols at the beginning of the list gave only low yields of phenylacetate with phenylacetyl trifluoroacetate, increased when the reactions were carried out in the presence of trifluoroacetic acid, while trifluoroethanol and phenol gave exclusively the phenylacetate esters. *tert.*-Butyl alcohol behaved as it did with acetyl trifluoroacetate, the yield of the phenylacetate

TABLE 4. *Reactions of phenylacetyl trifluoroacetate* (1·3 *mol.*) *with hydroxy-compounds* (2 *hr. at* ca. 20°).

R in ROH	RO·CO·CH_2Ph (%)	RO·CO·CF_3 (%)	+ CF_3·CO_2H (1·3 mol.) RO·CO·CH_2Ph (%)	+ CF_3·CO_2H (1·3 mol.) RO·CO·CF_3 (%)
Bu^n	16	84	28	71
$[CH_2]_5$>CH	28	71	56	44
Bu^s	35	63	58	42
p-NO_2·C_6H_4·CH_2	55	41	84	16
CF_3·CH_2	100	—	98	—
Ph	100	—	98	—
Bu^t	52	45	13	87

ester being decreased when the reaction was carried out in the presence of trifluoroacetic acid, suggesting that again the mechanism involved alkyl–oxygen fission of the tertiary alcohol.

DISCUSSION OF REACTION MECHANISMS.

General Behaviour of Acyl Trifluoroacetates.—In previous papers [3-6] it has been postulated that the unsymmetrical anhydride formed in considerable quantity when a carboxylic acid (R·CO_2H) is dissolved in trifluoroacetic anhydride is, in its molecular form, mainly a trifluoroacetylating agent. Further, however, it has been considered to be capable of dissociating slightly to give acylium (R·CO^+) and trifluoroacetate (CF_3·CO_2^-) ions, the former species being largely responsible for acylation, reacting with many compounds much more readily than the molecular anhydride is able to do. We still believe this to be true in general. It seems unlikely that other entities which might be present and capable of such a reaction, namely, the free carboxylic acid (R·CO_2H) and its symmetric anhydride [$(R·CO)_2O$], play a significant part in acylation in these systems. Both are in extremely small concentrations in an equimolecular mixture of a carboxylic acid and trifluoroacetic anhydride and the introduction of more trifluoroacetic acid should suppress the concentration of the symmetric anhydride [$(R·CO)_2O$] even further [7] [equilibrium (4)] although it probably would increase that of the acid (R·CO_2H) somewhat. The conjugate acids R·$CO_2H_2^+$, $(R·CO)_2·OH^+$, and $(R·CO·O·CO·CF_3·H)^+$, or any solvated species would be expected to break down to, or to react essentially as, acylium ions, and no attempt is made here to distinguish them. It seems likely however that the unsymmetrical anhydride in its molecular form may be an acylating agent in some specialised cases (see later).

The entities potentially capable of effecting trifluoroacetylation in the above systems containing unsymmetrical anhydrides are presumably trifluoroacetic anhydride, trifluoroacetic acid, trifluoroacetate anion (CF_3·CO_2^-), trifluoroacetylium cation (CF_3·CO^+), and the unsymmetrical anhydrides in their molecular forms. The first of these does not seem to be present in any appreciable concentration,[3] except possibly when a large excess of trifluoroacetic acid is introduced. Measurements of rates of reaction showed that trifluoroacetate esters were formed from the butyl alcohols and acetyl trifluoroacetate very much more rapidly than with trifluoroacetic acid, so that this acid can play only a minor rôle in trifluoroacetylation by the direct reaction. Alkyl–oxygen fission of a hydroxy-compound is a pre-requisite for reaction with the free trifluoroacetate anion (CF_3·CO_2^-), which must be associated with a cation, presumably acylium ion (R·CO^+). This type of fission has been demonstrated only with the specialised alcohols of group 2; otherwise it may be regarded as being of little importance. It seems unlikely that trifluoroacetylium cation (CF_3·CO^+) could exist in significant concentrations in these systems. It was inferred therefore that almost all of the trifluoroacetate esters formed arose from reactions of hydroxy-compounds with the molecular forms of the unsymmetrical anhydrides. From orthodox electronic theory the latter should be principally trifluoroacetylating

agents (cf. the work [8] on anhydrides from acetic and the chloroacetic acids), reacting always by acyl–oxygen fission.

Reactions of Acetyl Trifluoroacetate with Hydroxy-compounds of Sub-group 1*a*.—The mechanism suggested above is in general accord with the experimental results found with these systems. The rapidity of acylations of the types under discussion will presumably be determined largely by two factors, (*a*) the availability of electrons at the oxygen atom of the hydroxyl group, and (*b*) the accessibility of this group. Acetylations with the strongly electrophilic acetylium cation carrying a formal positive charge should not be influenced greatly by fine degrees of electron availability (*e.g.*, acetyl trifluoroacetate can acetylate [7] the hydroxyl group of acetic acid); and the steric factor, though obviously important, should be at a minimum with a fairly small attacking species such as this. In contrast, for trifluoroacetylations by molecular acetyl trifluoroacetate, since it is relatively less electrophilic and also larger, both factors (*a*) and (*b*) will be much more important. For the alcohols of sub-group 1a, however, neither factor should be sufficient to prevent the occurrence to an appreciable extent of this type of trifluoroacetylation. Though less reactive than the acetylium cation, molecular acetyl trifluoroacetate is present in vastly greater concentration. The order of increasing acetate : trifluoroacetate ratio in which the primary alcohols of sub-group 1a are arranged in Table 1 is that which would be predicted from simple electronic theory for increasing acidity, and hence presumably decreasing electron-availability on the oxygen atom of the un-ionised forms. *sec.*-Butyl alcohol and *cyclo*hexanol should be more basic than ethanol or butan-1-ol, but have much less accessible hydroxyl groups, so that the increased proportions of acetate obtained from the secondary alcohols can be explained by the greater difficulty of approach of molecular acetyl trifluoroacetate to the oxygen atom.

Addition of sodium trifluoroacetate to acetyl trifluoroacetate considerably decreased its acetylating power, presumably because of a decrease in the concentration of acetylium cations by a common-ion effect, which slowed the acetylation considerably. An inert non-polar solvent such as carbon tetrachloride (ε_{20} 2·23) should also decrease the overall ionisation and hence the proportion of acetate formed, again in accordance with the observed effects.

Trifluoroacetic acid promoted acetylation quite markedly with alcohols of this group. This obviously could not be a direct effect of normal dissociation of the acid on the ionisation of acetyl trifluoroacetate. The value for the dielectric constant [9] (ε_{20} 8·4) suggests that trifluoroacetic acid is not intrinsically a particularly highly ionising medium. Further, there is an indication of a maximum,[9b] well above the value for trifluoroacetic acid alone, in the dielectric constants of mixtures of acetic and trifluoroacetic anhydride. Thus it seems that the promotion of acetylation by the acid cannot be due merely to its properties as a polar solvent. Ready exchange of anions ($CF_3 \cdot CO_2^-$) between the acid and acetyl trifluoroacetate occurs almost certainly, since it has been demonstrated for the system acetyl trifluoroacetate–heptafluorobutyric acid. This could presumably give a transient liberation of acetylium cations, but need not necessarily, and in any case should not increase their overall concentration.

Trifluoroacetic acid is known to promote the polymerisation [10,11] of certain olefins such as styrene and α-methylstyrene. One reason for its high activity here may well be the ease with which it can solvate its own negative ions,[11] after initiation of the polymerisation by protonation, so that chain termination is inhibited. A very similar effect could well apply in our esterifications. The powerful influence of trifluoroacetic acid would then be due largely to its ability to solvate the asymmetric anhydride (this could be by addition to the fluorocarbonyl group, a process known to proceed readily in other

[8] Emery and Gold, *J.*, 1950, 1443, 1447, 1455.
[9] (*a*) Dannhauser and Cole, *J. Amer. Chem. Soc.*, 1952, **74**, 6105; (*b*) Tedder, *J.*, 1954, 2646.
[10] Bourne and Tatlow, unpublished observations.
[11] Throssell, Sood, Szwarc, and Stannett, *J. Amer. Chem. Soc.*, 1956, **78**, 1122.

connections, *e.g.*, hydration of fluoro-aldehydes and -ketones). Under ionising conditions, the actual liberation of a solvated anion would then be favoured with promotion of acylation by the acetylium cation released concomitantly.

Trifluoroacetic acid will presumably protonate the alcohol to some extent with consequent lower reactivity of the protonated species towards electrophilic reagents. It seems unlikely that this effect could assume major importance, however, since the acid will ionise only to a limited extent under these conditions.

Reactions of Acetyl Trifluoroacetate with Hydroxy-compounds of Sub-group 1b.—These hydroxy-compounds are all appreciably acidic (K_a values [12]: $CF_3 \cdot CMe_2 \cdot OH$, $2{\cdot}5 \times 10^{-12}$; $CF_3 \cdot CHMe \cdot OH$, $6{\cdot}3 \times 10^{-12}$; $CF_3 \cdot CH_2 \cdot OH$, $4{\cdot}0 \times 10^{-12}$; $C_6H_5 \cdot OH$, $1{\cdot}7 \times 10^{-10}$). Therefore, the electrons on the oxygen atoms of all these compounds should be relatively less readily available for interaction with weakly electrophilic reagents than is the case with the alcohols of sub-group 1a. Attack by molecular acetyl trifluoroacetate should thus be very slow. In fact, trifluoroacetyl esters are produced from members of sub-group 1b only in the presence of sodium trifluoroacetate. Also, the effect of added trifluoroacetic acid in speeding up reaction is most marked with these hydroxy-compounds.

The influence of accessibility of the hydroxyl group was shown very clearly in the measurements of the rates of reaction of acetyl trifluoroacetate with the fluoro-alcohols (of which the acidities do not differ greatly) to give acetate esters. The rates decreased markedly with increasing substitution of the carbon atom carrying the hydroxyl group. Further, the very profound effects exerted by a trifluoromethyl group on the properties of alcohols are well illustrated by a comparison of the behaviour of 2 : 2 : 2-trifluoro-1 : 1-dimethylethanol and of *tert.*-butyl alcohol (see below) towards acetyl trifluoroacetate–trifluoroacetic acid. In complete contrast to the latter, the tertiary fluoro-alcohol underwent no reactions involving alkyl–oxygen fission and behaved normally, but was rather unreactive, presumably because of both the steric effect and the electron-withdrawal by the fluorine atoms. This type of compound might well be employed usefully for studying steric factors of this type in general reactions of alcohols.

Reactions of Acetyl Trifluoroacetate with Hydroxy-compounds of Group 2.—Of the butyl alcohols, *tert.*-butyl alcohol should be the most basic but have the least accessible hydroxyl group. Reaction with acetyl trifluoroacetate in carbon tetrachloride was slower than for the isomers but gave a high proportion of acetate. This ester was also obtained in good yield in the reaction with acetyl trifluoroacetate–sodium trifluoroacetate. Some of the acetate produced will arise from attack by acetylium ion, of which however only a very low concentration should be present under these conditions of suppressed ionisation, so that an additional route to the acetate seems likely. It may well be that with an alcohol such as *tert.*-butyl alcohol, possessing an inaccessible hydroxyl group, in a reaction with molecular acetyl trifluoroacetate the relatively large trifluoromethyl group will hinder approach of the alcohol to the adjacent carbonyl group. The slower, but less hindered, attack on the acetyl group should then become of importance because of the reactivity of (electron-availability on) the hydroxyl group. Somewhat similar postulates have been made [8] to explain certain reactions of anhydrides of chloroacetic acids. This effect will probably be significant only with secondary and tertiary alcohols with both hindered and reactive hydroxyl groups (*i.e.*, not with members of group 1b) under essentially non-ionic conditions and should make only a very limited contribution to normal esterifications with trifluoroacetic acid present and inert solvents absent.

Under the reaction conditions so far discussed in this section esterification of *tert.*-butyl alcohol proceeded by normal acyl–oxygen fission. The behaviour of the alcohol with acetyl trifluoroacetate in the absence of a solvent or in the presence of trifluoroacetic acid was very different however. *tert.*-Butyl trifluoroacetate was a major product, particularly when the free acid was added, and a mechanism involving alkyl–oxygen fission at some stage was clearly indicated. However, both the acetate and the alcohol were attacked

[12] Henne and Pelley, *J. Amer. Chem. Soc.*, 1952, **74**, 1426.

by trifluoroacetic acid itself in the absence of solvents to give the trifluoroacetate ester. It is likely that these, particularly the first, are major routes to the last product in the esterifications with acetyl trifluoroacetate–trifluoroacetic acid. Presumably, in this type of reaction, the acid protonates the alcohol or acetate, and a neutral molecule (H_2O or HOAc) is then eliminated, the resultant carbonium cation finally reacting with a trifluoroacetate anion.

It is well known [13] that the phenyl group confers a greater degree of stability on carbonium ions than does a methyl group, and, as expected, L-1-phenylethanol and *tert.*-butyl alcohol behaved similarly. Under conditions of low acidity and suppressed ionisation *e.g.*, with carbon tetrachloride or sodium trifluoroacetate present, the L-alcohol gave appreciable amounts of acetate (behaviour similar to that of an alcohol at the end of sub-group **1a**), but no racemisation occurred. Racemisation was demonstrated only when trifluoroacetic acid was present; if it was liberated in the reaction, *i.e.*, no great amount was present, some optical activity was retained in the ester products. It seems very likely that in these systems only attack by a free perfluoro-carboxylic acid causes alkyl–oxygen fission and that acylium ions themselves do not. If they do, it is under conditions of high acidity when the acid itself will also give the same effect.

Diphenylmethanol, and its 4-methoxy-derivative which can give even more stabilised carbonium cations, afforded polymeric products very easily. Both gave considerable amounts of their trifluoroacetates even in the presence of much carbon tetrachloride, but the addition of trifluoroacetic acid considerably increased the yield of its esters.

These results are in general accord with data on the formation and hydrolysis of esters by processes involving alkyl–oxygen fission, of which full accounts of the mechanisms established have been given.[13] Direct evidence for the ionisation of tertiary alcohols, in an acidic medium, to give carbonium ions has been obtained [14] from cryoscopic measurements in concentrated sulphuric acid.

Esterifications with Benzoyl Trifluoroacetate.—Benzoyl trifluoroacetate showed much more tendency to give trifluoroacetates and thus presumably to react in its molecular form than did acetyl trifluoroacetate. A possible explanation of this is resonance stabilisation of the benzoylium cation ($C_6H_5 \cdot CO^+$) with consequent lowering of the density of the positive charge on the carbonyl group. This should slow down the reactions of the cation with hydroxy-functions and allow attack by the molecular anhydride to assume greater relative importance.

The acetylium cation cannot be stabilised in this way. Also, owing to the very slightly increased electronegativity, benzoyl trifluoroacetate may be a more reactive trifluoroacetylating agent than is acetyl trifluoroacetate. The greater size of the phenyl group than of methyl should also mean that steric factors would not favour benzoylation in this case.

It appeared that only in the presence of excess trifluoroacetic acid was benzoylation important with members of sub-group 1a, and that, even with those of sub-group 1b, trifluoroacetylation occurred to an appreciable extent. The rate of reaction of benzoyl trifluoroacetate with phenol in an excess of carbon tetrachloride to give the trifluoroacetate was decreased when trifluoroacetic acid was added. This could be due to solvation by the acid of the molecular anhydride.

Very many hydroxy-compounds are not normally acylated by processes involving alkyl–oxygen fission. For these, the following appear favourable conditions for use in reactions with carboxylic acid–trifluoroacetic anhydride: (*a*) the use of a stoicheiometric proportion of carboxylic acid to hydroxy-compound, with a slight excess of trifluoroacetic anhydride; (*b*) use of an excess of trifluoroacetic acid; (*c*) exclusion of any components

[13] Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 751; Davies and Kenyon, *Quart. Rev.*, 1955, **9**, 203.

[14] Newman, Craig, and Garrett, *J. Amer. Chem. Soc.*, 1949, **71**, 869; Newman and Deno, *ibid.*, 1951, **73**, 3644.

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which would give rise to any appreciable concentration of trifluoroacetate anions; (*d*) absence of non-polar solvents.

Experimental

Unless otherwise stated, dry reagents and anhydrous conditions were employed.

Preparation of Esters as Reference Compounds.—(a) *Trifluoroacetates.* With the exception of ethyl trifluoroacetate,[15] trifluoroacetate esters were prepared by treatment [16] of the corresponding hydroxy-compounds with trifluoroacetic anhydride–sodium trifluoroacetate. Four standard methods of isolation were evolved.

(i) The hydroxy-compound (1·0—3·3 g.) was treated with trifluoroacetic anhydride (1·3 mol.) and sodium trifluoroacetate (*ca.* 0·1 g.) and after the initial vigorous reaction had subsided, the mixture was heated under reflux for 15 min. Water (1 c.c.) was then added and the aqueous phase was neutralised rapidly with 2N-sodium hydroxide until it had pH 7—8 (Universal indicator). The organic phase was separated, dried ($MgSO_4$), filtered, and distilled.

TABLE 5. *Trifluoroacetate esters* ($R{\cdot}O{\cdot}CO{\cdot}CF_3$).

No.	R	Method	Yield (%)	B. p./mm.	n_D (t°)	Previous values B. p.	Previous values n_D (t°)	Ref.
I	Bu^n	ii	73	104°/745	1·3394 (18°)	102·7—102·8°	1·3391 (20°)	*a*
II	Bu^s	ii	57	93—94/740	1·3343 (18)	—	—	
III	Bu^t	i	62	85—86/750	1·3295 (19)	—	—	
IV	$[CH_2]_5{>}CH$	ii	76	150/759	1·3827 (19)	—	—	
V	Ph	iii	86	147/750	1·4197 (20)	146·5—147·0	1·4183 (25)	*b*
VI	$Ph{\cdot}CH_2$	iii	82	177—178/755	1·4363 (18)	173—174/760	—	*c*
VII	Ph·CHMe	iv	80	73/15	1·4329 (22)	—	—	
VIII	$Ph_2{\cdot}CH$	iv	79	131/13	1·5030 (19)	—	—	
IX	*p*-MeO·C_6H_4·CHPh	iv	79	167/13	1·5107 (19)	—	—	
X	$CF_3{\cdot}CH_2$		21	55·5/752	1·280 (20)	55	1·2812 (20)	*d*
XI	$CF_3{\cdot}CHMe$	i	52	63—64/746	1·291 (16)	—	—	
XII	$CF_3{\cdot}CMe_2$	i	19	73/743	1·3080 (20)	—	—	

No.	Formula	Required (%) C	H	F	equiv.	Found (%) C	H	F	equiv.
I	$C_6H_9O_2F_3$	42·4	5·3	—	170	42·7	5·3	—	170
II	,,	,,	,,	—	,,	42·5	5·5	—	172
III	,,	,,	,,	33·5	,,	42·1	5·2	32·9	171
IV	$C_8H_{11}O_2F_3$	49·0	5·65	29·1	196	49·5	5·7	28·9	200
VII	$C_{10}H_9O_2F_3$	55·05	4·2	26·1	218	55·5	4·0	25·8	217
VIII	$C_{15}H_{11}O_2F_3$	64·3	4·0	—	280	64·2	3·9	—	282
X	$C_4H_3O_2F_3$	24·5	1·0	—	196	24·8	1·35	—	195
XI	$C_5H_4O_2F_3$	28·6	1·9	—	210	28·8	2·0	—	209
XII	$C_6H_6O_2F_3$	32·2	2·7	—	224	32·5	2·9	—	220

IX Stable only for 15 min. after isolation.

XII Purified by preparative-scale gas chromatography.[a]

p-Nitrobenzyl trifluoroacetate [16] had m. p. 47°.

(*a*) Campbell, Knobloch, and Campbell, *J. Amer. Chem. Soc.*, 1950, **72**, 4380. (*b*) Clark and Simons, *ibid.*, 1953, **75**, 6305. (*c*) Weygand and Leising, *Chem. Ber.*, 1954, **87**, 248. (*d*) Swarts, *Bull. Soc. chim. Belg.*, 1934, **43**, 471. (*e*) Evans and Tatlow, *J.*, 1955, 1184.

(ii) The neutral aqueous phase was extracted with ether, and the extract was dried ($MgSO_4$), filtered, and distilled through a short Vigreux column to give ether and then the trifluoroacetate.

[15] Gilman and Jones, *ibid.*, 1943, **65**, 1458.

[16] Bourne, Tatlow, and Tatlow, *J.*, 1950, 1367.

(iii) Direct distillation through a short Vigreux column afforded a mixture of trifluoroacetic acid and the excess of anhydride, and then the trifluoroacetate.

(iv) Trifluoroacetic anhydride (1·3 mol.) was added slowly to a cooled solution of the hydroxy-compound in ether (5 c.c.) and, after 10 min. at 20°, ether (25 c.c.) was added. The solution was washed with sodium hydrogen carbonate solution, then with water, dried ($MgSO_4$), filtered, and distilled under reduced pressure, to give the trifluoroacetate.

The experimental details are given in Table 5. The *esters* to which no references are given are new. The equivalents were determined by hydrolysis with excess of alkali and back-titration.

(b) *Acetates, benzoates, and phenylacetates.* Many of these were available commercially or were prepared by standard methods. The benzoates of the fluorine-containing hydroxy-compounds, and 2 : 2 : 2-trifluoroethyl phenylacetate, were prepared by treatment of the hydroxy-compound with the appropriate acid chloride in pyridine. 2 : 2 : 2-*Trifluoroethyl benzoate* (84%) had b. p. 83°/19 mm., n^{16} 1·4508 (Found: C, 52·9; H, 3·5%; equiv., 202. $C_9H_7O_2F_3$ requires C, 52·95; H, 3·5%; equiv., 204); 2 : 2 : 2-*trifluoro*-1-*methylethyl benzoate* (87%) had b. p. 88°/20 mm., n^{17} 1·4476 (Found: C, 55·0; H, 4·2%; equiv., 217. $C_{10}H_9O_2F_3$ requires C, 55·05; H, 4·2%; equiv., 218); 2 : 2 : 2-*trifluoro*-1 : 1-*dimethylethyl benzoate* (50%) had b. p. 93°/18 mm., n^{15} 1·4523 (Found: C, 56·9; H, 4·8%; equiv., 230. $C_{11}H_{11}O_2F_3$ requires C, 56·9; H, 4·8%; equiv., 232); 2 : 2 : 2-*trifluoroethyl phenylacetate* (57%) had b. p. 99·5°/15 mm., n^{19} 1·4467 (Found: C, 55·4; H, 4·4%; equiv., 214).

Absorption Bands Used in the Infrared Spectroscopic Analysis.—The infrared spectra of the esters in carbon tetrachloride (*ca.* 0·08M) were determined over the range 1700—1900 cm.$^{-1}$, by use of a Grubb-Parsons spectrometer with a rock-salt prism. The frequencies (cm.$^{-1}$) of the carbonyl absorption bands and the optical densities (O.D. of M-solutions in a cell of thickness *ca.* 0·1 mm.) of the esters are given in Table 6.

TABLE 6. *Infrared analysis of esters.*

	RO·CO·CF_3		ROAc		ROBz		RO·CO·CH_2Ph	
R	cm.$^{-1}$	O.D.	cm.$^{-1}$	O.D.	cm.$^{-1}$	O.D.	cm.$^{-1}$	O.D.
Et	1786	6·8	1743	7·0	1723	7·6	—	—
Bu^n	1787	7·3	1735	6·6	1723	6·6	1736	6·4
Bu^s	1779	7·2	1733	7·1	1719	7·9	1735	6·6
Bu^t	1777	7·8	1736	5·8	1715	7·1	1735	6·3
$[CH_3]_2$>CH	1777	7·2	1734	6·3	1720	8·1	1739	6·4
Ph	1795	7·2	1764	5·7	1740	7·6	1755	4·2
Ph·CH_2	1776	6·9	1749	5·7	1726	7·2	—	—
Ph·CHMe	1783	6·7	1738	4·6	—	—	—	—
Ph_2CH	1786	7·2	1741	6·2	—	—	—	—
p-MeO·C_6H_4·CHPh	1786	6·3	1741	5·0	—	—	—	—
p-NO_2·C_6H_4·CH_2	1789	7·1	1755	5·7	1729	7·3	1749	5·6
CF_3·CH_2	1802	3·6	1764	4·4	1740	7·1	1761	4·3
CF_3·CHMe	1790	4·7	1754	5·3	1729	7·1	—	—
CF_3·CMe_2	1792	6·1	1752	5·9	1727	6·8	—	—

Reactions of Acetyl Trifluoroacetate with Hydroxy-compounds.—The hydroxy-compound (*ca.* 0·0025 mole) was treated with acetyl trifluoroacetate (1·3 mol.) for 2 hr. at 20° and then carbon tetrachloride (10 c.c.) was added. The solution was washed with sodium hydrogen carbonate solution, and the organic layer, together with extracts of the aqueous phase, was dried ($MgSO_4$), filtered, and diluted to 25 c.c. with carbon tetrachloride. The infrared spectrum of the solution (ester concentration *ca.* 0·1M) was then determined over the frequency range 1700—1900 cm.$^{-1}$. A comparison of the calculated optical densities (M-hydroxy-compound in a cell of thickness *ca.* 0·1 mm.), at the appropriate frequencies, with those of solutions of the pure acetate and trifluoroacetate enabled the proportion of each ester produced in the reaction to be determined. To check the accuracy of the method a mixture of ethyl acetate and ethyl trifluoroacetate in carbon tetrachloride (each 0·08M) was submitted to the same procedure. Recoveries of 97% and 96% respectively were observed. It was also shown that acetic and trifluoroacetic acid, the by-products of the reaction, were completely removed by the extraction process. The accuracy of the analysis is estimated at ±5%. The results of the reactions of

a number of hydroxy-compounds with acetyl trifluoroacetate alone and in the presence of trifluoroacetic acid, carbon tetrachloride, carbon tetrachloride–trifluoroacetic acid, and sodium trifluoroacetate are given in Table 1.

In the reactions in carbon tetrachloride (columns III and IV), with ethanol, butan-1-ol, and *tert.*-butyl alcohol, some reactions were done with amounts of trifluoroacetic acid below 1·3 mol. The products obtained had the expected compositions, intermediate between those in columns III and IV.

Rates of Reaction of Hydroxy-compounds with Acetyl Trifluoroacetate and with Acetyl Trifluoroacetate–Trifluoroacetic Acid.—A 0·1M-carbon tetrachloride solution (25 c.c.) of the hydroxy-compound was kept in a thermostat at 25° ± 0·1° for 1 hr. before acetyl trifluoroacetate (1·3 mol.) was added with thorough mixing. Samples (*ca.* 2 c.c. each) were withdrawn at noted time intervals during 1 hr., and plunged into sodium hydrogen carbonate solution with vigorous shaking. After separation and drying ($MgSO_4$) the samples were analysed for ester content as before. A similar experiment was carried out in which acetyl trifluoroacetate (1·3 mol.) and trifluoroacetic acid (1·3 mol.) were added. The results, in the form: time of reaction (min.), acetate ester produced (%), trifluoroacetate ester produced (%), respectively in each case, are given below for the reaction of hydroxy-compounds with (A) acetyl trifluoroacetate and (B) acetyl trifluoroacetate–trifluoroacetic acid:

Bu^nOH. (A) 0·5, 4, 64; 1, 5, 74; 3, 6, 86; 6, 6, 89; 17, 6, 89; 60, 6, 90.
(B) 0·5, 3, 58; 1, 6, 68; 2, 8, 75; 4, 9, 78; 8, 9, 85; 15, 9, 90; 60, 9, 90.

Bu^sOH. (A) 0·5, 8, 14; 1, 10, 18; 2, 11, 25; 4, 22, 36; 8, 25, 47; 15, 27, 62; 30, 28, 67; 60, 30, 67.
(B) 0·5, 7, 14; 1, 8, 19; 2, 10, 28; 4, 17, 39; 8, 22, 47; 15, 24, 60; 30, 27, 65; 60, 30, 68.

Bu^tOH. (A) 2, 0, 0; 4, 5, 0; 8, 9, 0; 16, 18, 1; 32, 27, 3; 60, 50, 4.
(B) 2, 7, 0; 4, 13, 0; 8, 18, 0; 16, 30, 1; 32, 54, 2; 60, 70, 4.

$C_6H_5{\cdot}CH_2{\cdot}OH$. (A) 1, 12, 32; 2, 14, 48; 4, 18, 62; 6, 18, 70; 8, 18, 71; 15, 18, 78; 29, 18, 80.
(B) 1, 12, 49; 2, 18, 58; 4, 21, 61; 6, 23, 64; 8, 23, 67; 15, 28, 70; 29, 28, 71.

$[CH_2]_5{>}CH{\cdot}OH$. (A) 1, 15, 20; 2, 19, 23; 4, 23, 33; 9, 30, 49; 15, 32, 51; 30, 33, 56; 45, 34, 61; 58, 35, 64.
(B) 1, 14, 22; 2, 16, 25; 4, 17, 33; 9, 24, 51; 15, 28, 54; 30, 32, 61; 45, 33, 65; 58, 33, 67.

PhOH. (A) 2, 16, 0; 4, 21, 0; 8, 33, 0; 18, 61, 0; 28, 81, 0; 38, 86, 0; 48, 88, 0; 58, 90, 0.
(B) 2, 47, 0; 4, 68, 0; 8, 79, 0; 18, 88, 0; 28, 91, 0; 38, 93, 0; 48, 95, 0; 58, 96, 0.

$CF_3{\cdot}CH_2{\cdot}OH$. (A) 1, 14, 0; 2, 18, 0; 4, 30, 0; 8, 45, 0; 15, 57, 0; 30, 75, 0; 45, 84, 0; 60, 91, 0.
(B) 1, 23, 0; 2, 34, 0; 4, 52, 0; 8, 73, 0; 15, 84, 0; 30, 89, 0; 45, 93, 0; 60, 98, 0.

$CF_3{\cdot}CHMe{\cdot}OH$. (A) 2, 2, 0; 4, 4, 0; 8, 8, 0; 17, 15, 0; 28, 23, 0; 38, 31, 0; 48, 40, 0; 58, 50, 0.
(B) 2, 12, 0; 4, 21, 0; 8, 29, 0; 17, 50, 0; 28, 60, 0; 38, 67, 0; 48, 73, 0; 58, 79, 0.

$CF_3{\cdot}CMe_2{\cdot}OH$. (A) 2, 0, 0; 4, 0, 0; 8, 0, 0; 15, 2, 0; 25, 3, 0; 35, 10, 0; 45, 15, 0; 55, 21, 0.
(B) 2, 3, 0; 4, 6, 0; 8, 14, 0; 15, 26, 0; 25, 39, 0; 35, 51, 0; 45, 63, 0; 55, 67, 0.

The yields in each series after 60 min. are given in Table 1, columns V and VI.

Rates of Reaction of Trifluoroacetic Acid with the Butyl Alcohols.—The butyl alcohols in carbon tetrachloride (0·1M; 25 c.c.) were treated with trifluoroacetic acid (1·3 mol.), and the ester produced determined in the manner described before for the reactions with acetyl trifluoroacetate. With *n*-butyl alcohol, the yields of trifluoroacetate ester after 2·3, 4·0, 6·3, and 8·0 hr., were 25%, 41%, 58%, and 69% respectively. With *sec.*-butyl alcohol they were 6%, 15%,

25%, and 33%, whilst with *tert.*-butyl alcohol no trifluoroacetate was detected even after 4 days.

Reaction of L-1-*Phenylethanol with Acetyl Trifluoroacetate, Acetyl Trifluoroacetate–Trifluoroacetic Acid, and Trifluoroacetic Acid.*—The hydrogen phthalate of DL-1-phenylethanol was resolved with L-brucine according to Houssa and Kenyon's method,[17] and on hydrolysis with 2N-sodium hydroxide afforded L-1-phenylethanol (23%), b. p. 98°/20 mm., n_D^{18} 1·5264, α_D^{19} −20·45° (*l* 0·5), $[\alpha]_D^{20}$ −42·8° (*c* 2·48 in EtOH), $[\alpha]_D^{20}$ −53·5° (*c* 2·58 in $CHCl_3$). Houssa and Kenyon [17] gave b. p. 93°/14 mm., α_{5893}^{20} −10·94° (*l* 0·25).

Prepared in the same way as the DL-ester, L-1-phenylethyl trifluoroacetate (87%) had b. p. 74°/15 mm., n_D^{19} 1·4328, $\alpha_D^{21\cdot5}$ −66·15° (*l* 0·5), $[\alpha]_D^{19}$ −110·0° (*c* 2·20 in $CHCl_3$), $[\alpha]_D^{19}$ −114·3° (*c* 1·49 in CCl_4) (Found: C, 55·5; H, 4·0; F, 25·8%; equiv., 217. Calc. for $C_{10}H_9O_2F_3$: C, 55·0; H, 4·1; F, 26·1%; equiv. 218). Hydrolysis of the L-trifluoroacetate afforded L-1-phenylethanol (82%), b. p. 95—96°/15 mm., $n_D^{18\cdot5}$ 1·5233, α_D^{16} −20·35° (*l* 0·5), $[\alpha]_D^{19}$ −42·4° (*c* 2·31 in EtOH), $[\alpha]_D^{19}$ −53·1° (*c* 2·41 in $CHCl_3$).

Acetylation of the L-alcohol with acetic anhydride and pyridine afforded L-1-phenylethyl acetate (70%), b. p. 99°/18 mm., n_D^{20} 1·4923, α_D^{20} −58·23° (*l* 0·5), $[\alpha]_D^{21}$ −105·2° (*c* 3·84 in EtOH), $[\alpha]_D^{21}$ −104·7° (*c* 4·26 in $CHCl_3$) (Found: C, 73·1; H, 7·3%; equiv., 166. Calc. for $C_{10}H_{12}O_2$: C, 73·1; H, 7·4%; equiv., 164). Hydrolysis gave L-1-phenylethanol (86%), b. p. 96°/18 mm., $n_D^{18\cdot5}$ 1·5239, α_D^{22} −20·14° (*l* 0·5), $[\alpha]_D^{22}$ −42·2° (*c* 2·18 in EtOH), $[\alpha]_D^{22}$ −53·1° (*c* 3·84 in $CHCl_3$). Cited values [18] for the DL-acetate were b. p. 88°/10 mm., n_D^{18} 1·5003.

The acetate and trifluoroacetate were separable chromatographically on carefully neutralised aluminium oxide. Neutralisation of the aluminium oxide was effected by heating it under reflux for 30 min., first with a 20% solution of ethyl formate in light petroleum (b. p. 60—80°) and then with a 2% solution of ethyl trifluoroacetate in the same solvent. The oxide was filtered and dried before use. In a trial separation a mixture of the esters (0·5 g. each) in light petroleum (5 c.c.) was put on to a column of neutralised aluminium oxide (100 g.; 33 × 2·5 cm.) which was then eluted with light petroleum (b. p. 60—80°). The trifluoroacetate ester in the eluate was identified by its absorption band at 1786 $cm.^{-1}$ and when this had been removed completely from the column, the acetate was eluted with ether. The esters were isolated by distillation and recoveries of 70% and 87% respectively were obtained.

The experimental details of the reactions of L-1-phenylethanol with acetyl trifluoroacetate, acetyl trifluoroacetate–trifluoroacetic acid, and trifluoroacetic acid are given in Table 2, as are control experiments in which the L-acetate and the L-trifluoroacetate esters were treated with the same reactants. The changes in optical rotations of the reaction mixtures with time were observed. If, after the requisite period, the reaction mixture could have contained only one ester (as when the L-alcohol and the L-trifluoroacetate were treated with trifluoroacetic acid) it was dissolved in ether and the solution was washed with dilute sodium hydrogen carbonate solution. After drying ($MgSO_4$), the organic phase was filtered and distilled under reduced pressure, to give the required ester which was examined polarimetrically. If the reaction mixture could have contained both acetate and trifluoroacetate esters, a small portion, sufficient to give a total ester concentration of 0·1M, was withdrawn, diluted to 2 c.c. with carbon tetrachloride, and analysed by infrared spectroscopy for ester content as previously described. The remainder of the reaction mixture was dissolved in ether and washed with dilute sodium hydrogen carbonate solution, dried ($MgSO_4$), filtered, and evaporated to give a mixture of esters which was separated on a column of neutralised aluminium oxide (100 g.; 33 × 2·5 cm.) as described above. The optical activities were then determined. In some cases, the esters were hydrolysed and the properties of the alcohols also measured.

When the L-acetate and L-trifluoroacetate were treated with acetic acid or acetic anhydride there was no change either in the composition or in the optical activity.

Reactions of Benzoyl and of Phenylacetyl Trifluoroacetate with Hydroxy-compounds.—The results are recorded in Tables 3 and 4 for the reactions of a number of hydroxy-compounds with benzoyl and with phenylacetyl trifluoroacetate, which were carried out in the same way as with acetyl trifluoroacetate.

Rates of Reaction of Hydroxy-compounds with Benzoyl Trifluoroacetate and with Benzoyl Trifluoroacetate–Trifluoroacetic Acid.—These were carried out as for acetyl trifluoroacetate. Results are given for time of reaction (min.), benzoate ester produced (%), trifluoroacetate

[17] Houssa and Kenyon, *J.*, 1930, 2260.
[18] Olsson, *Z. phys. Chem.*, 1928, **133**, 293.

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ester produced (%), respectively, for the reaction of each hydroxy-compound with (A) benzoyl trifluoroacetate and (B) benzoyl trifluoroacetate–trifluoroacetic acid.

$Bu^{n}OH$. (A) 1, 0, 93; 2, 0, 99; 15, 0, 99.
(B) 1, 0, 93; 2, 0, 100; 15, 0, 100.
PhOH. (A) 2, 0, 39; 4, 0, 42; 8, 0, 44; 15, 1, 53; 30, 3, 57; 45, 3, 61; 60, 3, 67.
(B) 2, 0, 14; 4, 1, 15; 8, 3, 18; 15, 4, 18; 30, 7, 26; 45, 7, 31; 60, 8, 36.

Anhydride Systems involving Acetyl Heptafluorobutyrate.—(a) *Acetyl heptafluorobutyrate from acetic anhydride–heptafluorobutyric anhydride.* An infrared spectroscopic analysis of this system was impossible over the frequency range 1000—1250 cm.$^{-1}$ because of the close proximity of absorption bands of acetic anhydride (1121 cm.$^{-1}$), heptafluorobutyric anhydride (1134 cm.$^{-1}$), and acetyl heptafluorobutyrate (1126 cm.$^{-1}$). The analysis was possible however in carbon tetrachloride (*ca.* 0·1M in a cell of thickness *ca.* 0·1 mm.) over the frequency range 1700—1900 cm.$^{-1}$. The absorption bands of heptafluorobutyric anhydride (1799 and 1864 cm.$^{-1}$) and of acetic anhydride (1761 and 1829 cm.$^{-1}$) were entirely absent from the spectrum of an equimolecular mixture of acetic and heptafluorobutyric anhydrides which had been warmed at 40° for 15 min., and were replaced by bands (1780 and 1853 cm.$^{-1}$) which were characteristic of acetyl heptafluorobutyrate.

(b) *Equilibria in the systems acetyl trifluoroacetate–heptafluorobutyric acid and acetyl heptafluorobutyrate–trifluoroacetic acid.* The infrared analysis of these systems was carried out in carbon tetrachloride (*ca.* 0·05M) over the frequency range 1000—1250 cm.$^{-1}$ by using the bands at 1072 cm.$^{-1}$ and 1126 cm.$^{-1}$ for the analysis of acetyl trifluoroacetate and acetyl heptafluorobutyrate respectively. The calculated optical densities (M in a cell of thickness *ca.* 0·1 mm.) of the appropriate solutions were then used to estimate by comparison the proportion of each of these unsymmetrical anhydrides in mixtures of acetyl trifluoroacetate–heptafluorobutyric acid, and acetyl heptafluorobutyrate–trifluoroacetic acid. Heptafluorobutyric acid showed a weak absorption band (1125 cm.$^{-1}$) which interfered with the estimation of acetyl heptafluorobutyrate (1126 cm.$^{-1}$), and the latter absorbed weakly over the range 1063—1085 cm.$^{-1}$ which interfered with the estimation of acetyl trifluoroacetate. Allowance was made for these absorptions when estimating the proportions of the unsymmetrical anhydride compounds. The results are recorded in Table 7; the accuracy of the method is estimated as ±10%.

TABLE 7. *Infrared spectroscopic analysis of the system*

$$AcO{\cdot}CO{\cdot}CF_3 + C_3F_7{\cdot}CO_2H \rightleftharpoons AcO{\cdot}CO{\cdot}C_3F_7 + CF_3{\cdot}CO_2H$$

Original components (mol.)				Components measured	
$AcO{\cdot}CO{\cdot}CF_3$	$C_3F_7{\cdot}CO_2H$	$AcO{\cdot}CO{\cdot}C_3F_7$	$CF_3{\cdot}CO_2H$	$AcO{\cdot}CO{\cdot}CF_3$ (1072 cm.$^{-1}$)	$AcO{\cdot}CO{\cdot}C_3F_7$ (1126 cm.$^{-1}$)
1·0	0·5	—	—	0·7	0·3
1·0	1·0	—	—	0·55	0·45
1·0	2·0	—	—	0·3	0·7
—	—	1·0	0·5	0·3	0·7
—	—	1·0	1·0	0·5	0·5
—	—	1·0	2·0	0·65	0·35

(c) *Reaction of acetyl trifluoroacetate–heptafluorobutyric acid with phenetole.* A mixture of phenetole (0·483 g.), acetyl trifluoroacetate (0·925 g.), and heptafluorobutyric acid (1·24 g.) was kept at 20° for 3 hr. After dilution of the solution with water (1 c.c.), and neutralisation with sodium hydroxide, *p*-ethoxyacetophenone was isolated as its semicarbazone (78%); m. p. and mixed m. p. 182°.

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THE CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.
THE CHEMISTRY DEPARTMENT, ROYAL HOLLOWAY COLLEGE,
ENGLEFIELD GREEN, SURREY.

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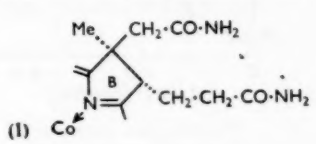
670. *Chemistry of the Vitamin B_{12} Group. Part VII.* The Products of Chromic Acid Oxidation.*

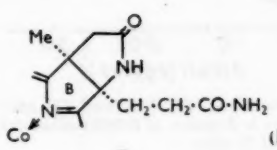
By V. M. Clark, A. W. Johnson, I. O. Sutherland, and Sir Alexander Todd.

Chromic acid oxidation of dehydrovitamin B_{12} and the hexacarboxylic acid (V), but not of vitamin B_{12} or its acid degradation products, yields a new imide-lactam shown to have structure (VI). The isolation of this product confirms the presence of an extra ring both in dehydrovitamin B_{12} and in the products of vigorous alkaline hydrolysis of the vitamin.

In the elucidation [1,2] of the structure of vitamin B_{12} oxidative studies have been of importance, for, depending on the conditions used for oxidation, it is possible either (i) to modify the macrocyclic system in the vitamin, *e.g.*, in the formation of dehydrovitamin B_{12} (cf. I ⟶ II) [2] wherein the acetamido-residue of ring B has undergone cyclisation to give the *cis*-fused pyrrolidone, or (ii) to disrupt the molecule, whereby a variety of aliphatic acids are obtained together with the succinimide (III; R = NH_2) and the related lactone [3] (IV). The substituted succinimides (III; R = OH) and (IV) were first obtained as optically inactive products from the oxidation of acid-hydrolysed vitamin B_{12} using sodium dichromate in acetic acid; however, the vitamin itself yields optically active (III; R = NH_2) in addition to (IV).



(I)



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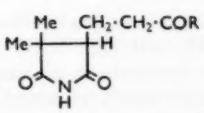

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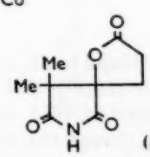


(IV)

We now report an extended study of this type of oxidation using chromic acid in aqueous acetic acid, the substrates being vitamin B_{12}, dehydrovitamin B_{12}, and the hexabasic acid (V) arising from vigorous alkaline hydrolysis of the vitamin.[4] Both the vitamin and the hexabasic acid yield the lactone (IV) whereas, under the same conditions, it has proved impossible to convert amide or acid (III; R = NH_2 or OH) into this lactone (IV).[5] Formation of the *spiro*-lactone by oxidation is presumably akin to that of the lactone produced by halogenation of vitamin B_{12},[2] *i.e.*, cyclisation occurs at an early stage in the oxidative process.

Initial experiments on oxidation of the hexabasic acid (V) yielded both the acid (III; R = OH) and the lactone (IV), together with a third product, $C_{10}H_{12}O_5N_2$, which also appeared to be an imide. The products (III) and (IV) are obviously derived from ring C of the macrocycle, and, whilst it would not be expected that rings A and D would readily yield succinimides, ring B might be the source of similar oxidation products.[6] The

* Part VI, *J.*, 1957, 1168.

[1] Hodgkin, Pickworth, Robertson, Trueblood, Prosen, and White, *Nature*, 1955, **176**, 325; Bonnett, Cannon, Johnson, Sutherland, Todd, and Lester Smith, *ibid.*, p. 328.

[2] Bonnett, Cannon, Clark, Johnson, Parker, Lester Smith, and Todd, *J.*, 1957, 1158.

[3] Kuehl, Shunk, and Folkers, *J. Amer. Chem. Soc.*, 1955, **77**, 251; Kuehl, Shunk, Moore, and Folkers, *ibid.*, p. 4418.

[4] Bonnett, Cannon, Johnson, and Todd, *J.*, 1957, 1148.

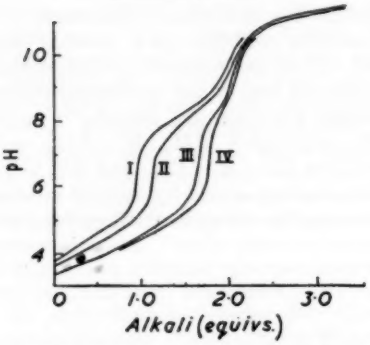
[5] Dr. K. Folkers, personal communication.

[6] Cf. Ficken, Johns, and Linstead, *J.*, 1956, 2272, 2280.

presence of two nitrogen atoms in this new oxidation product derived from the hexacarboxylic acid (V) led us to believe that the product had structure (VI) and, in this paper, we present evidence in support of this view. As might be expected, this new material has also been observed among the products of oxidation of dehydrovitamin B_{12} (II) and other alkaline hydrolysis products of the vitamin, but not from the vitamin itself or from its acid degradation products: these observations are in accordance with our previously postulated dependence of the ring B cyclisation upon alkaline oxidative conditions.

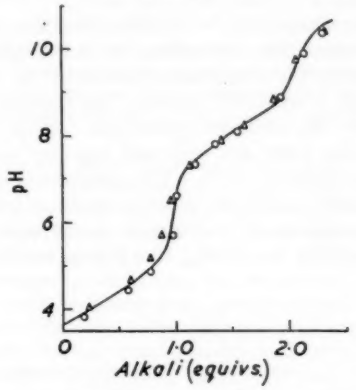
The infrared spectrum of the new product contained bands in the carbonyl region at

FIG. 1. *Alkaline hydrolysis of the oxidation product.*



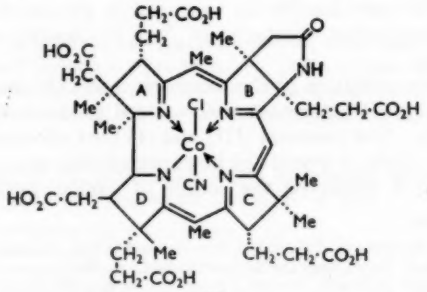
I, Initial titration; II, III, and IV after exposure to 3 *equivs. of* 0·003N-*alkali for* 2, 9, *and* 22 *days.*

FIG. 2. *Titration of the oxidation product.*



△ *Back-titration against acid.*
○ *Re-titration against alkali.*

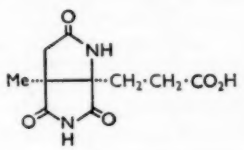
1775, 1723, and 1700 cm.$^{-1}$ (Nujol mull) closely analogous to the bands at 1776 and 1709 cm.$^{-1}$ (Nujol mull) of the succinimide (III; R = OH), although in the former case there was an additional intense band at 1655 cm.$^{-1}$. The spectrum in dioxan solution did not contain the 1655 cm.$^{-1}$ band though the other carbonyl bands remained at 1780 and 1727 cm.$^{-1}$. In this solution spectrum we assign these bands to the carbonyl groups of the imide, with the lactam-carbonyl absorption superposed upon the 1727 cm.$^{-1}$ band. That the spectrum of the new degradation product was consonant with structure (VI) rather than (VII) was clear from a comparison of its infrared spectrum with that of α-acetamidoglutarimide which exhibited bands at 1747, 1664, and 1623 cm.$^{-1}$ (KBr disc).



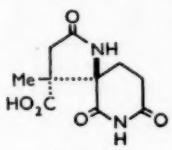
(V)

On treatment with aqueous barium hydroxide, the oxidation product slowly liberated one mole of ammonia: the course of hydrolysis was also followed by electrometric titration

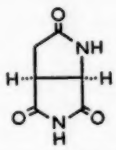
and after three weeks in the presence of three equivalents of 0·003N-sodium hydroxide solution the compound was almost completely converted into a dicarboxylic acid (Fig. 1), a change corresponding to the cleavage of the succinimide to the succinamic acid. Electrometric titration of a dilute aqueous solution of the oxidation product gave a completely reversible curve (Fig. 2), showing the presence of two acidic groups within the molecule, the apparent pK_a values being 4·4 and 8·1.* Treatment with diazomethane gave a neutral dimethyl compound: this new compound shows only the lactam N–H stretching frequency in the infrared region (original product, 3340, 3180, 3080 cm.$^{-1}$; dimethyl derivative 3200, 3090 cm.$^{-1}$) and gives, on alkaline hydrolysis, methylamine, indicating that the original oxidation product contained an acidic >N–H group. This sequence of methylation, followed by the liberation of methylamine on alkaline hydrolysis, was also observed with



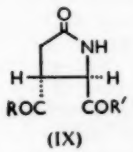
(VI)



(VII)



(VIII)



(IX)

succinimide,[7] and with the lactone-imide (IV). The *cis*-fused pyrrolidone-succinimide (VIII) could also be methylated with diazomethane though lack of material prevented study of the subsequent hydrolysis.

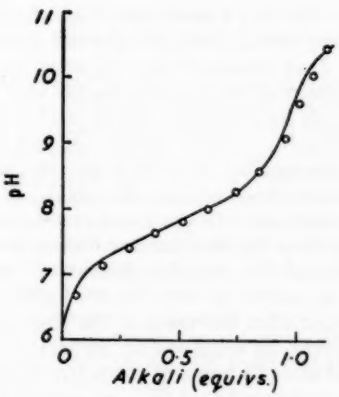


FIG. 3. *Titration of 4-hydroxy-3 : 3-dimethyl-2 : 5-dioxopyrrolidine-4-propionic lactone.*

Continuous line—forward-titration against alkali. ○ *Back-titration against acid.*

Of the two pK_a values, that of 4·4 evidently corresponds to the carboxyl group in structure (VI), whilst that of 8·1 must relate to the >NH of the succinimide. The pK_a values of succinimides usually lie within the range 8·8—9·7 (see Table 1), being approximately two units more acidic than glutarimide (pK_a' = 11·2).[8]

Comparison of the values for compounds (IV) and (VIII) with the others suggests that the enhancement of acidity is related (i) to substitution by a more electronegative atom and (ii) to a specific geometrical disposition of the carbonyl dipoles in the imide and lactone or lactam system, since neither acyclic amido-substitution (compound 3) nor a fused carbocyclic ring (compounds 5, 6, 7) has an analogous effect.

The close similarity of the oxidation product and compound (VIII) on electrometric

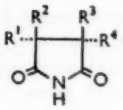
* pK_a values refer to the pH recorded at 20° by a Pye glass electrode and meter of an aqueous solution at the half-neutralisation point. The meter was standardised with aqueous buffer at pH 7.

[7] Labruto, *Gazzetta*, 1933, **63**, 266.

[8] Kornfeld, Jones, and Parke, *J. Amer. Chem. Soc.*, 1949, **71**, 150.

titration is paralleled in their ultraviolet spectra. Succinimides usually exhibit an absorption maximum at ~240 mμ (ε ~120),[9] but the oxidation product has $\lambda_{max.}$ 254 mμ (ε 364) and (VIII) has $\lambda_{max.}$ 252 mμ (ε 233). We therefore feel justified in concluding that our oxidation product $C_{10}H_{12}O_5N_2$ is correctly represented by structure (VI).

TABLE 1. pK_a *values for succinimides*



No.	R^1	R^2	R^3	R^4	pK_a
1	H	H	H	H	9·70 [a]
2	H	H	H	NH_2	9·0 [b]
3	H	H	H	NHAc	8·85
4	Me	Me	Me	Me	9·7
5	H	*cis*-$[CH_2]_3$		H	9·63
6	H	*cis*-$[CH_2]_3$		H	9·53
7	H	*cis*-$[CH_2]_4$		H	9·72
Compound (IV)	Me	Me	*spiro*-Butyrolactone		7·9 *
Compound (VIII)	H	*cis*-2 : 3-Pyrrolid-5-one		H	8·15

All values refer to aqueous solution and are reproducible to ±0·05 unit.

* The reversible nature of the curves obtained in the titration of this compound (Fig. 3) shows the acidity attributable to the loss of a proton rather than the opening of the lactone ring.

[a] Schwarzenbach and Lutz, *Helv. Chim. Acta*, 1940, **23**, 1162. [b] Sondheimer and Holley, *J. Amer. Chem. Soc.*, 1954, **76**, 2467.

The closest analogue to the oxidation product so far synthesised is compound (VIII). Triethyl 1-aminoprop-1-ene-1 : 2 : 3-tricarboxylate,[10] on reduction with hydrogen and Raney nickel, gave diethyl *trans*-5-oxopyrrolidine-2 : 3-dicarboxylate (IX; R = R′ = OEt). That intramolecular acylation (*i.e.*, lactam formation) had occurred in preference to formation of the dioxopiperazine was confirmed by a molecular-weight determination. Hydrolysis by ethanolic sodium hydroxide gave the sodium salt of the monoester (IX; R = OEt, R′ = OH),* which, on treatment with ammonia gave the ammonium salt of the monoamide; conversion into the acid and esterification by diazomethane then gave the *trans*-amido-ester (IX; R = NH_2, R′ = OMe).

The cyclisation of succinamic esters to succinimides under alkaline conditions proceeds readily; thus Sondheimer and Holley [11] obtained a 90% yield in three minutes using an aspartic acid (*i.e.*, acyclic) derivative. However, compounds (IX) were *trans*, the diacid giving no anhydride even under forcing conditions, and cyclisation to the succinimide must occur after inversion at the ring carbon atom bearing the methoxycarbonyl group. In the event, by using sodium methoxide in methanol, a 57% yield of the imide (VIII) was obtained after 24 hours at room temperature.

It is of interest that the new oxidation product (VI), 1-2′-carboxyethyl-5-methyl-2 : 7-diaza*bicyclo*[3 : 3 : 0]octane-3 : 6 : 8-trione, should be optically active. A 5% solution showed no detectable rotation in sodium light but at 365 mμ it had [α] −68·6°.

EXPERIMENTAL

Oxidation of the Hexacarboxylic Acid Degradation Product (V) *of Vitamin* B_{12}.—To a well-stirred solution of the hexabasic acid (3·972 g.) in acetic acid (250 ml.) at 20° was added, during 45 min., a solution of chromic acid (12·03 g.) in water (100 ml.). After 1 hr. at room temperature the solution was slowly heated during 4 hr. to 100° and kept at that temperature for

* Assignment of direction of preferential hydrolysis based on the behaviour of *N*-acylaspartic acids [11] and the observed pK_a values.[12]

[9] Cf. Saidel, *Nature*, 1953, **172**, 955.
[10] Wislicenus and Waldmüller, *Ber.*, 1911, **44**, 1566.
[11] Sondheimer and Holley, *J. Amer. Chem. Soc.*, 1954, **76**, 2467.
[12] Clayton, Kenner, and Sheppard, *J.*, 1956, 371.

2 hr. Excess of chromic acid was then reduced by ethanol (40 ml.), the solution evaporated to dryness under reduced pressure, and the residue dissolved in 0·5N-sulphuric acid (350 ml.). The acid solution was continuously extracted with ether for two successive periods of 5 days to give extracts I and II respectively.

Extract I was evaporated and an aqueous solution of the residue allowed to percolate through a column of Amberlite I.R.-120 resin (H^+ form) in order to remove small quantities of inorganic cations. Removal of the solvent gave a colourless gum (1·122 g.) which was further purified by counter-current distribution between ether and water. After 31 transfers at 20° the following fractions were obtained, the contents of each tube being examined by paper chromatography, by the ascending method with ethanol–ammonia (*d* 0·88)–water (20 : 1 : 4) as solvent on Whatman no. 1 paper; the chromatograms were developed with Universal indicator. Fraction *A* (455 mg.; tubes 1—2), gum, R_F 0·23, 0·05; *B* (134 mg.; tubes 3—8), gum, R_F 0·20; *C* (325 mg.; tubes 9—16), gum R_F 0·46; *D* (146 mg.; tubes 17—31), colourless non-acidic crystals. Fraction *A* was combined with the product from extract II (see below). Fraction *B* did not crystallise, contained neither an amide nor an imide, and was not further examined. After 3 recrystallisations from water, fraction *C* had m. p. 140—141°, alone or mixed with synthetic DL-3 : 3-dimethyl-2 : 5-dioxopyrrolidine-4-propionic acid (Found: C, 54·5; H, 6·0; N, 7·0. Calc. for $C_9H_{13}O_4N$: C, 54·3; H, 6·6; N, 7·0%). The infrared spectra of the oxidation product and the synthetic compound were identical over the range 4000—650 cm.$^{-1}$.

After two crystallisations from water, fraction *D* had m. p. 150—151°, undepressed on admixture with synthetic DL-4-hydroxy-3 : 3-dimethyl-2 : 5-dioxopyrrolidine-4-propionic lactone (Found: C, 54·8; H, 5·7; N, 7·05. Calc. for $C_9H_{11}O_4N$: C, 54·8; H, 5·6; N, 7·1%). The infrared spectra of the oxidation product and the synthetic compound were identical over the range 4000—650 cm.$^{-1}$. Methylation of the lactone in methanolic solution with ethereal diazomethane (1 mol.) gave *4-hydroxy-1 : 3 : 3-trimethyl-2 : 5-dioxopyrrolidine-4-propionic lactone*, m. p. 104° after recrystallisation from benzene–light petroleum (b. p. 40—60°) and sublimation at 100°/0·2 mm. (Found: C, 57·1; H, 6·1; N, 6·7. $C_{10}H_{13}O_4N$ requires C, 56·9; H, 6·2; N, 6·65%).

Extract II was combined with fraction *A* from extract I and subjected to 33 transfers at 25° between ethyl acetate and water. The contents of each tube were evaporated and examined by paper chromatography as before. The following fractions were taken: *E* (137 mg.; tubes 1—2), green gum, R_F 0·21, 0·05; *F* (370 mg.; tubes 3—6), colourless crystals, R_F 0·23; *G* (133 mg.; tubes 7—10), R_F 0·16, 0·23, 0·48. Fraction *E* contained inorganic material and was not examined further. Fraction *F* was recrystallised twice from water; then it had m. p. 213—214° (Found: C, 49·8; H, 5·2; N, 11·65%; equiv., 250. $C_{10}H_{12}O_5N_2$ requires C, 50·0; H, 5·05; N, 11·65%; equiv., 240), main infrared bands (Nujol mull) 3340, 3180, 3080, 2920, 2750, 2550, 2500, 1775, 1723, 1706, 1655, 1432, 1390, 1348, 1330, 1317, 1282, 1268, 1225, 1157, 1127, 1103, 967, 807, 755; (dioxan solution) 3170, 3080, 1780, 1727 cm.$^{-1}$.

Fraction *G* was combined with the residue obtained from the mother-liquors of fraction *F* and subjected to a further counter-current distribution with the system water–acetic acid–ethyl acetate (25 : 8 : 25). After 39 transfers at 20° a substance (115 mg.; *K* 0·55) was obtained in tubes 8—20 which was identical with that obtained from fraction *F*.

Comparison of Oxidation of Dehydrovitamin B_{12}, and Alkaline and Acid Hydrolysis Products of Vitamin B_{12}.—Chromic acid (67·3 mg.) in water (1·5 ml.) was added to a stirred solution of the substance (21·7 mg.) in acetic acid (5 ml.) at 20°, and after 2 hr. the solution was slowly heated to 100° during 4 hr. and kept at that temperature for 2 hr. Excess of chromic acid was reduced by ethanol (0·5 ml.) and, after evaporation, the residue was continuously extracted with ether from 0·5N-sulphuric acid (30 ml.) for 48 hr. The ethereal solution, on evaporation, gave a green gum (11·8 mg.) which was examined by paper chromatography with the solvent systems: (*a*) *tert.*-butyl alcohol–acetic acid–water (5 : 2 : 3); (*b*) ethanol–ammonia (*d* 0·88)–water (20 : 1 : 4).

Dehydrovitamin B_{12} and the hexacarboxylic acid from the alkaline hydrolysis of the vitamin gave products A, B, C, and D; the heptacarboxylic acid from the acid hydrolysis of the vitamin gave products A, C, D, and E.

Product A, R_F 0·05 in system (*b*), was an unidentified acid.

Product B, R_F 0·71 in system (*a*), 0·25 in (*b*), was an acid and an amide or imide,[13] identifiable as the compound in fraction *F* above.

[13] Rydon and Smith, *Nature*, 1952, **169**, 922; Reindel and Hoppe, *Chem. Ber.*, 1954, **87**, 1103.

XUM

Product C, R_F 0·84 in system (*a*), 0·48 in (*b*), was an acid and an amide or imide, identified as DL-3 : 3-dimethyl-2 : 5-dioxopyrrolidine-4-propionic acid.

Product D, R_F 0·18 in system (*b*), was an unidentified acid.

Product E, R_F 0·77 in system (*a*), 0·31 in (*b*), was an acid and an amide or imide, unidentified.

Reactions of the compound from fraction F. (*a*) Methylation. A methanolic solution of the product (10 mg. in 1 ml.) from the foregoing experiment reacted rapidly with ethereal diazomethane and consumed 2·05 mols. of the reagent. After evaporation of the solvent, the residue was recrystallised from hot ethyl acetate (0·5 ml.) by adding light petroleum (1 ml.; b. p. 40—60°); the *product* had m. p. 149° (hot stage) (Found: N, 10·2. $C_{12}H_{16}O_5N_2$ requires N, 10·4%).

(*b*) Hydrolysis. The compound (39·8 mg.) from fraction *F* was heated in 10% aqueous barium hydroxide (10 ml.) on the water-bath, in a stream of nitrogen, and the ammonia evolved was collected in an excess of standard sulphuric acid. After 78 hr. evolution of ammonia (0·92 mol.) had ceased.

The above methylated product (3 mg.) was heated in 20% aqueous sodium hydroxide (5 ml.) on the water-bath. The evolved gases were collected, as before, in excess of hydrochloric acid and after 12 hr. the experiment was discontinued and the acidic solution evaporated to dryness. Examination of the residue by paper chromatography with the system butan-1-ol–acetic acid–water (4 : 1 : 5) revealed a spot (R_F 0·28) corresponding to methylamine (R_F of authentic sample 0·28) after development with ninhydrin.

L-N-*Acetylaspartimide.*—L-*N*-Benzyloxycarbonylaspartimide [11] (302 mg.) in acetic anhydride (15 ml.) was hydrogenated at room temperature over palladium black (50 mg.). The product (201 mg.) recrystallised from ethanol, to give L-N-*acetylaspartimide*, m. p. 162—164° (decomp.), $[\alpha]_D^{20}$ −56·6° (Found: C, 45·8; H, 5·1; N, 17·9. $C_6H_8O_3N_2$ requires C, 46·15; H, 5·15; N, 17·95%), main infrared bands (KBr disc) 3425, 3240, 3070, 1792, 1724, 1634, 1575, 1555, 1376, 1362, 1333, 1302, 1276, 1236, 1199, 1170, 1130, 1040, 1018, 926, 893, 810 cm.$^{-1}$.

DL-α-*Acetamidoglutarimide.*—L-*N*-Acetylglutamic acid [14] (3·0 g.) was dissolved in acetic anhydride at 100° and after 30 min. the solvent was evaporated; the residual colourless gum, in chloroform solution, was treated with gaseous ammonia whereupon crystals of the ammonium salts of *N*-acetylglutamine and *N*-acetyl*iso*glutamine separated. The mixed salts (2·0 g.) were dissolved in acetic anhydride at 100° and after 20 min. the solvent was evaporated and the residue extracted into ethyl acetate from an aqueous solution brought to pH 7 by means of sodium hydrogen carbonate. Removal of the ethyl acetate gave the *product* (300 mg.) which crystallised as needles, m. p. 180°, from ethyl acetate–*n*-hexane (Found: C, 49·2; H, 5·7; N, 16·3. $C_7H_{10}O_3N_2$ requires C, 49·4; H, 5·9; N, 16·5%), main infrared bands (KBr disc) 3390, 3195, 3067, 1745, 1681, 1623, 1408, 1381, 1337, 1305, 1274, 1242, 1138, 1047, 1026, 990, 954, 873, 844 cm.$^{-1}$.

Triethyl 1-*Aminoprop*-1-*ene*-1 : 2 : 3-*tricarboxylate.*—Dry ammonia was passed through a solution of diethyl ethoxalylsuccinate (50 g.) in dry ether (250 ml.). The precipitated ammonium salt was separated and kept in a vacuum-desiccator over solid potassium hydroxide for 7 days. Recrystallisation of the product from ethanol gave the amino-ester, m. p. 68° (32 g., 65%) as colourless needles (Found: C, 52·7; H, 7·1; N, 5·15. Calc. for $C_{12}H_{19}O_6N$: C, 52·7; H, 7·0; N, 5·15%), main infrared bands (Nujol mull) 3405, 3300, 2980, 1723, 1665, 1613, 1538, 1487, 1466, 1448, 1408, 1392, 1369, 1343, 1293, 1233, 1185, 1162, 1093, 1024, 955, 915, 864, 837, 777, 725; ($CHCl_3$ solution) 3470, 3310, 1739, 1673, 1600 cm.$^{-1}$.

Diethyl trans-5-*Oxopyrrolidine*-2 : 3-*dicarboxylate.*—The foregoing ester (15 g.) in ethanol (50 ml.) was hydrogenated at 120°/100 atm. for 7 hr. over Raney nickel (*ca.* 7 g.). After removal of catalyst and solvent, the residue was distilled under reduced pressure and the fraction of b. p. 170—180°/0·5 mm. representing the *pyrrolidine ester* was collected. The viscous oil (7 g., 57%) crystallised after several weeks and after 2 recrystallisations from ethyl acetate–light petroleum (b. p. 40—60°) had m. p. 48·5—50° [Found, on a fraction of b. p. 177°/0·5 mm.: C, 52·1; H, 6·7; N, 5·9%; *M* (Rast), 217. $C_{10}H_{15}O_5N$ requires C, 52·4; H, 6·6; N, 6·1%; *M*, 229], main infrared bands (Nujol mull) 3180, 3090, 1739, 1726, 1703, 1673, 1488, 1355, 1291, 1268, 1233, 1217, 1200, 1176, 1117, 1083, 1039, 1027, 862, 799, 763, 730, 680; (dioxan solution) 3250, 1737, 1721 cm.$^{-1}$.

This diester (1·14 g.) was dissolved in 4% aqueous sodium hydroxide (10 ml.) at 100°. After 45 min., the solution was cooled and percolated through a column of Dowex 50 (H^+ form);

[14] Nicolet, *J. Amer. Chem. Soc.*, 1930, **52**, 1192.

evaporation of the acidic eluate gave a colourless gum which slowly crystallised. From ethanol–benzene the *diacid* separated as colourless prisms (700 mg., 81%), m. p. 210° (Found: C, 41·8; H, 4·2; N, 8·3%; equiv., 89. $C_6H_7O_5N$ requires C, 41·6; H, 4·1; N, 8·1%; equiv., 86·5), main infrared bands (Nujol mull) 3220, 1765, 1715, 1645, 1327, 1248, 1170, 1084, 1020, 959, 752, 703, 658 cm.$^{-1}$.

trans-3-*Ethoxycarbonyl-5-oxopyrrolidine-2-carboxylic Acid.*—The above pyrrolidine diester (1·02 g.) was dissolved in cold ethanolic sodium hydroxide (0·2 g., in 10 ml.); the monosodium salt was precipitated at room temperature in 15 min. The mixture was diluted with water (20 ml.) and percolated through Dowex 50 (H^+ form). The percolate was evaporated and the residue recrystallised from ethyl acetate, to give the *monocarboxylic acid* (630 mg., 70%) as colourless prisms, m. p. 153°, raised to 160—161° by 2 recrystallisations from water (Found: C, 47·5; H, 5·6; N, 7·05%; equiv., 195. $C_8H_{11}O_5N$ requires C, 47·75; H, 5·5; N, 7·0%; equiv., 201). Titration in aqueous solution indicated an apparent pK_a 3·5. Main infrared bands were at (Nujol mull) 3190, 3060, 2970, 2900, 2600, 2520, 1733, 1652, 1475, 1455, 1417, 1377, 1357, 1270, 1244, 1220, 1187, 1117, 1086, 1040, 1014, 957, 920, 876, 857, 756, 720, 692; (dioxan solution) 3250, 1737, 1721 cm.$^{-1}$.

trans-2-*Methoxycarbonyl-5-oxopyrrolidine-3-carboxyamide.*—The acid ester (630 mg.) from the previous experiment was dissolved in methanol (25 ml.) saturated with ammonia and kept for 5 days at room temperature. Removal of the solvent gave a crystalline ammonium salt which was converted into the free acid by allowing its aqueous solution to percolate through Dowex 50 (H^+ form). After evaporation of the eluate, the *amic acid* was obtained as a colourless gum which crystallised on being scratched. Two recrystallisations from 95% ethanol gave the acid (400 mg., 70%) as prisms, m. p. 191° (Found: C, 42·0; H, 5·0; N, 16·4%; equiv., 175. $C_6H_8O_4N_2$ requires C, 41·85; H, 4·7; N, 16·3%; equiv., 172). Titration in aqueous solution indicated an apparent pK_a 3·0; main infrared bands (Nujol mull) were at 3395, 3300, 3180, 1725, 1661, 1615, 1299, 1255, 1224, 1172, 1096, 1027, 910, 835, 669 cm.$^{-1}$.

The corresponding *methyl ester*, obtained in 46% yield by use of diazomethane in ether–methanol and recrystallised from acetone, had m. p. 159—160° (Found: C, 45·6; H, 5·4; N, 15·35. $C_7H_{10}O_4N_2$ requires C, 45·15; H, 5·4; N, 15·05%), main infrared bands (Nujol mull) 3385, 3290, 3175, 3070, 1739, 1699, 1665, 1614, 1384, 1294, 1263, 1230, 1204, 1115, 1038, 1016, 996, 909, 799, 777, 659; (dioxan solution) 3270, 1746, 1714, 1701 cm.$^{-1}$.

cis-5-*Oxopyrrolidine-2 : 3-dicarboxyimide.*—The above *trans*-amide ester (465 mg.) was kept in a solution of sodium methoxide (270 mg.) in dry methanol (25 ml.) for 24 hr. at room temperature, then diluted with water (25 ml.) and percolated through Dowex 50 (H^+ form). Electrometric titration of the eluate indicated that it consisted of 55% of the required imide, together with free carboxylic acid. The solution was evaporated, and the residual gum dissolved in water (10 ml.) and percolated through Dowex 1 × 2 (acetate form). The solvent was removed from the eluate to give colourless crystals of the required *imide* (220 mg., 57%), m. p. 240—241° (decomp.) after recrystallisation from ethanol (Found: C, 46·6; H, 4·15; N, 18·25%; equiv., 152. $C_6H_6O_3N_2$ requires C, 46·75; H, 3·9; N, 18·2%; equiv., 154), main infrared bands (Nujol mull) 3270, 3130, 3060, 2980, 2760, 1775, 1725, 1708, 1687, 1672, 1436, 1425, 1395, 1357, 1324, 1250, 1202, 1168, 1107, 1088, 1044, 1004, 995, 955, 860, 807, 758, 717, 670; (dioxan solution) 3240, 1730 cm.$^{-1}$.

cis-1-*Methyl-5-oxopyrrolidine-2 : 3-dicarboxyimide.*—The imide (50 mg.) from the foregoing experiment was dissolved in a minimum of methanol and an excess of ethereal diazomethane was added. After 30 min., solvent was removed to give the N-*methyl compound* (25 mg., 46%), m. p. 185—186° (decomp.) after 2 recrystallisations from ethyl acetate (Found: C, 50·0; H, 5·5; N, 16·45. $C_7H_8O_3N_2$ requires C, 50·0; H, 4·8; N, 16·65%), main infrared bands (Nujol mull) 3335, 2980, 2940, 2860, 1779, 1710, 1474, 1442, 1420, 1387, 1321, 1286, 1254, 1127, 1094, 1060, 1034, 976, 882, 826, 777, 731, 700; (dioxan solution) 3250, 1787, 1720 cm.$^{-1}$.

We are grateful to the Department of Scientific and Industrial Research for a Maintenance Allowance (held by I. O. S.) and to Glaxo Laboratories Ltd. for vitamin B_{12}.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, April 18th*, 1958.]

XUM

671. *Complexes of Thiourea containing Tellurium.*

By E. E. Aynsley and W. A. Campbell.

Thiourea forms with tellurium tetrahalides four types of compound, *viz.*, $(CSN_2H_4)_2TeX_4$, $(CSN_2H_5)_2TeX_6$, $(CSN_2H_5)_2TeX_6.2CSN_2H_5X$, and disubstitution compounds of the form $(CSN_2H_3)_2TeX_2$. The last are deposited from ethanol and in the process the solvent is converted into the corresponding ethyl halide.

Urea forms with tellurium tetrahalides unstable urea–tetrahalogenotellurium(IV) complexes and stable uronium pentahalogenotellurites, $(CON_2H_5)TeX_5$.[1] Thiourea and tellurium tetrahalides react quite differently and the products depend upon solvent and the relative concentrations of the reactants.

Dithiourea–tetrahalogenotellurium(IV) complexes, $(CSN_2H_4)_2,TeX_4$ where X = Cl or Br, were prepared by mixing solutions of thiourea and the corresponding tellurium tetrahalide in acetone or in acetic acid, and by shaking solid thiourea (which is insoluble in ether) with ethereal solutions of the tellurium tetrahalides.

Attempts to isolate these compounds from ethanol solutions produced instead diamidinothiodihalogenotellurium(IV) compounds $(CSN_2H_3)_2TeCl_2$ and $(CSN_2H_3)_2TeBr_2$, and ethyl halides. The bromo-compound was formed quantitatively, but the chloro-compound was always obtained mixed with some dithiourea–tetrachlorotellurium(IV), $(CSN_2H_4)_2TeCl_4$.

That $(CSN_2H_3)_2TeCl_2$ and $(CSN_2H_3)_2TeBr_2$ are formed by bonding between the tellurium atom of the halide and the sulphur atom of the thiourea molecule is to be expected from the known properties of thiourea and is proved as follows: when *S*-benzylthiourea reacts with tellurium tetrachloride or tetrabromide in ethanol, *S*-benzylthiourea–tetrahalogenotellurium(IV) compounds, $Ph{\cdot}CH_2{\cdot}SCN_2H_3,TeX_4$, are precipitated instead of compounds similar to the dihalogeno-compounds above. Thus the latter are probably formed by way of a two-step scheme:

$$TeX_3\overset{+}{\overset{-}{X}} + \overset{+}{H}\text{–}\overset{-}{S}{\cdot}C(:NH){\cdot}NH_2 \longrightarrow TeX_3\text{–}S{\cdot}C(:NH){\cdot}NH_2 + HX$$

$$\overset{-}{X}TeX_3\text{–}S{\cdot}C(:NH){\cdot}NH_2 + \overset{+}{H}\text{–}\overset{-}{S}{\cdot}C(:NH){\cdot}NH_2 \longrightarrow TeX_3[{\cdot}S{\cdot}C(:NH){\cdot}NH_2]_2 + HX$$

followed by subsequent reaction between the hydrogen halide and ethanol to produce an ethyl halide and water. Infrared spectroscopy also supports this structure for $(CSN_2H_3)_2TeX_2$.

The reaction could proceed by way of the addition compound $(CSN_2H_4)_2,TeX_4$ followed by elimination of two molecules of hydrogen halide. This was shown to be unlikely because when $(CSN_2H_4)_2TeBr_4$ was boiled with ethanol $(CSN_2H_3)_2TeBr_2$ was formed extremely slowly.

Water is produced in the reaction and this could cause some hydrolysis of $(CSN_2H_3)_2TeX_2$ or of unchanged tellurium halide. We have shown that these compounds are unaffected by prolonged boiling with ethanol containing small traces of water, provided there is always excess of thiourea present, and that tellurous acid is soluble in the same mixture. Since in our experiments these compounds were always prepared by use of excess of thiourea (thiourea is readily removed by hot ethanol), our samples of $(CSN_2H_3)_2TeX_2$ were not contaminated by decomposition products.

Dithiuronium hexachlorotellurite, $(CSN_2H_5)_2TeCl_6$, can be prepared by mixing solutions of thiourea and tellurium tetrachloride in acetic acid saturated with dry hydrogen chloride. The bromo-analogue is best prepared by cooling hydrobromic acid solutions containing thiourea and a large excess of tellurium tetrabromide.

From the solutions obtained by boiling thiourea and tellurium tetrahalide (or dioxide

[1] Aynsley and Campbell, *J.*, 1956, 832.

with the appropriate halogen acid the double salts $(CSN_2H_5)_2TeCl_6,2CSN_2H_5Cl$ and $(CSN_2H_5)_2TeBr_6,2CSN_2H_5Br$ have been isolated. Tellurium compounds of this type have not previously been reported. They can also be prepared by boiling $(CSN_2H_3)_2TeX_2$ with excess of the appropriate halogen acid, showing that tellurium tetrahalides and thiuronium halides must have been re-formed. This suggests that the reactions between tellurium tetrahalides and thiourea are reversible. In ethanol removal of the hydrogen halide to form ethyl halide favours the formation of the diamidinothiodihalogeno-compounds; in acetic acid, acetone, and ether the hydrogen halide is not removed so that the dihalogeno-compounds are not formed in these solvents.

Experimental

Analysis.—Tellurium was weighed as the element after reduction of the complex with sulphur dioxide and hydrazine; nitrogen was determined by the micro-Dumas method, and chlorine, bromine, and iodine (as silver salts), fluorine (as lead chlorofluoride), and sulphur (as barium sulphate) by the micro-Parr bomb method.

Dithiourea-tetrahalogenotellurium(IV).—(*a*) Thiourea (1 g.) and tellurium tetrachloride (3 g.), each in acetic acid (100 ml.), were mixed. *Dithiourea-tetrachlorotellurium*(IV) separated immediately as a yellow powder and was dried *in vacuo* (yield 2·6 g.), m. p. 175° (decomp.) [Found: Te, 29·7; Cl, 34·8; N, 13·2. $(CSN_2H_4)_2TeCl_4$ requires Te, 30·2; Cl, 33·7; N, 13·3%]. Addition of water to the solid causes blackening owing to the formation of hydrogen sulphide and consequent reduction to tellurium. (*b*) Thiourea (0·4 g.) and tellurium tetrabromide (1·5 g.), each in acetone (200 ml.), were mixed. *Dithiourea-tetrabromotellurium*(IV) was precipitated (yield 1·5 g.) as an orange-yellow power, m. p. 210° (decomp.) [Found: Te, 22·3; Br, 52·9; N, 9·8. $(CSN_2H_4)_2TeBr_4$ requires Te, 21·2; Br, 53·4; N, 9·4%], which blackens when added to water. These compounds were also prepared by shaking powdered thiourea (insoluble in ether) with excess of an ethereal solution of the appropriate tetrahalide. In the chloride preparation the thiourea first formed a lumpy red-brown solid which on further shaking crumbled to a yellow powder. In both cases the bulk of the thiourea increased remarkably as reaction proceeded.

Diamidinothiodihalogenotellurium(IV).—Thiourea (1 g.) and tellurium tetrabromide (4 g.) were refluxed with ethanol (200 ml.) for 2 hr. *Diamidinothiodibromotellurium*(IV) was precipitated (2·6 g.) as a yellow powder, m. p. 215° (decomp.) [Found: Te, 29·2; Br, 36·5; N, 12·8. $(CSN_2H_3)_2TeBr_2$ requires Te, 29·1; Br, 36·6; N, 12·8%]. With tellurium tetrachloride (1·5 g.) in place of the tetrabromide, a pale yellow powder was obtained with a Te : Cl atomic ratio of 1 : 2·5 [Found: Te, 33·0; Cl, 22·9; N, 14·4. Calc. for $(CSN_2H_3)_2TeCl_2$: Te, 36·5; Cl, 20·4; N, 13·1%]. This was a mixture of $(CSN_2H_3)_2TeCl_2$ and $(CSN_2H_4)_2TeCl_4$, which accounts for the high Te : Cl ratio. Both materials blacken on addition of water and effervesce vigorously with nitric acid, evolving oxides of nitrogen.

The same compounds were also slowly precipitated when cold alcoholic solutions of thiourea and the tellurium tetrahalide were mixed and set aside. A third method of preparation is to reflux the hexahalogenotellurites with ethanol.

In each case fractional distillation of the ethanol mother liquor yielded an ethyl halide in quantities sufficient to account for the halogen removed from the tellurium tetrahalide. Free acid was not detected in the distillate.

Infrared Examination of $(CSN_2H_3)_2TeX_2$.—The infrared spectra, measured in potassium bromide discs between 2 and 15 μ, are very similar. A broad absorption band in the 3 μ region due to N–H stretching vibrations shows maxima at 3348, 3313, 3274, 3168, 3127 cm.$^{-1}$ (cf. crystalline thiourea: 3394, 3287, 3184, 3099 cm.$^{-1}$). Thiourea shows a weak absorption band at 2686 cm.$^{-1}$, which can probably be assigned to S–H stretching. A weaker maximum at 2716 cm.$^{-1}$ occurs for the sample of the dibromide (which is probably a mixture) and not for the dichloride: this lends some support to the view that there is Te–S bonding. Peaks at 1635 (s), 1618 (s), 1519 (sh), 1400 (m), 1362 (sh), 1166 (w), 1099 (w), 1031 (w), 720 (w), and 684 (m) cm.$^{-1}$ (all measured with a rock-salt prism) are shown by the dibromide : values for the dichloride are practically identical. For thiourea, well-defined maxima occur at 1621 (s), 1470 (m), 1414 (s), 1085 (m), and 731 (s) cm.$^{-1}$. The band at 1635 cm.$^{-1}$ may be assigned [2] to >C=NH, not present

[2] Weissberger, "Techniques of Organic Chemistry," Vol. IX., "Chemical Applications of Spectroscopy," Interscience, New York, 1956, p. 532.

in crystalline thiourea: that at 1618 cm.$^{-1}$, due to C–NH_2, occurs in both. The band at 1470 cm.$^{-1}$ in thiourea, but not present in the dibromide, may be assigned to the N–C=S group.[3] These considerations further support Te–S–C(:NH)·NH_2 as the mode of attachment of the thiourea residue.

Dithiuronium Hexahalogenotellurites.—(*a*) Thiourea (1 g.) and tellurium tetrachloride (3 g.), each dissolved in acetic acid (100 ml.) saturated with dry hydrogen chloride, were mixed, the flask remaining connected to the hydrogen chloride supply. Lemon-yellow plates of dithiuronium hexachlorotellurite were immediately formed. On exposure to air these darkened, depositing tellurium. Since the compound was too unstable for ordinary analysis, it was washed quickly (twice) with acetic acid and, while still wet, transferred to a weighed beaker of water, and the atomic ratio of tellurium to chlorine determined [Found: Te : Cl = 1 : 6].

(*b*) Thiourea (0·5 g.) in concentrated hydrobromic acid (100 ml.) was added to tellurium tetrabromide (3 g.) in 100 ml. of the same acid and the solution boiled. To the hot red solution was added a 10-fold excess (25 g.) of tellurium tetrabromide, which caused the liquid to become dark red. After this was kept overnight, dark red crystals of *dithiuronium hexabromotellurite* separated. Though more stable than the hexachlorotellurite, these crystals decomposed rapidly on drying, but in addition to a determination of the atomic ratio Te : Br as described above, an analysis was attempted [Found: Te : Br ratio = 1 : 6. Te, 17·1; Br, 63·8. $(CSN_2H_5)_2TeBr_6$ requires Te, 16·8; Br, 63·3%]. It is inconvenient to prepare this compound by use of acetic acid saturated with dry hydrogen bromide as solvent owing to the low solubility of tellurium tetrabromide in this liquid.

(*c*) Dithiuronium hexabromotellurite (1 g.) was boiled with concentrated hydriodic acid. Some iodine and tellurium tetraiodide were produced and after being filtered and cooled the solution deposited *dithiuronium hexaiodotellurite* as dark crystals resembling potassium permanganate (4·2 g.). It had m. p. 145° (decomp.) [Found: Te, 11·5; I, 74·0. $(CSN_2H_5)_2TeI_6$ requires Te, 12·2; I, 73·1%].

Double Salts of Dithiuronium Hexahalogenotellurites and Thiuronium Halides.—(*a*) Thiourea (2 g.) and tellurium dioxide (2 g.) were boiled with excess of concentrated hydrochloric acid, and the resulting solution was rapidly filtered. The orange filtrate, on cooling, deposited greenish-yellow crystals of a mixture of unstable $(CSN_2H_5)_2TeCl_6$ with the double salt of this compound and thiuronium chloride. These crystals rapidly darkened in air owing to separation of tellurium, and were discarded. The lemon-yellow mother liquor slowly deposited lemon-yellow crystals of the *double salt*. This material, m. p. 148° (decomp.), is quite stable in air [Found: Te, 17·9; Cl, 38·7; N, 15·8. $(CSN_2H_5)_2TeCl_6,2CSN_2H_5Cl$ requires Te, 17·7; Cl, 39·5; N, 15·6%].

(*b*) With concentrated hydrobromic acid in place of hydrochloric acid, the resulting red solution yielded two quantities of orange crystals which were mixtures but the third and subsequent lots of crystals were the bright red, stable, pure *double salt*, m. p. 155° (decomp.) [Found: Te, 11·8; Br, 59·9; N, 10·5. $(CSN_2H_5)_2TeBr_6,2CSN_2H_5Br$ requires Te, 12·0; Br, 60·3; N, 10·5%].

(*c*) Both double salts were also made by dissolving 1 equiv. of dithiuronium hexachlorotellurite or hexabromotellurite and 2 equiv. of thiourea in the minimum of hot halogen acid and allowing the solution to cool, or by boiling $(CSN_2H_5)_2TeCl_2$ with concentrated hydrochloric acid and $(CSN_2H_5)_2TeBr_2$ with concentrated hydrobromic acid and allowing the solutions to cool.

S-*Benzylthiourea–tetrabromotellurium*(IV).—*S*-Benzylthiuronium chloride (10 g.) was suspended in ethanol, surrounded by a solid carbon dioxide–alcohol freezing mixture, and treated with sodium (1 g.) to liberate the base. After ½ hr., tellurium tetrabromide (25 g.) in ethanol was added. Yellow, amorphous S-*benzylthiourea–tetrabromotellurium*(IV) was precipitated [Found: Te, 20·0; Br, 53·7; N, 4·05. $C_7H_7SCN_2H_4,TeBr_4$ requires Te, 20·7; Br, 53·5; N, 4·65%].

Di-S-benzylthiuronium Hexahalogenotellurites.—When *S*-benzylthiourea, liberated from its hydrochloride as described above, was warmed with the theoretical quantity of tellurium dioxide and excess of the appropriate concentrated halogen acid, di-*S*-benzylthiuronium hexahalogenotellurites were formed: *-fluoro-*, unstable white plates which rapidly turn yellow in air [Found: Te, 22·5; F, 19·0; N, 10·1. $(C_7H_7SCN_2H_5)_2TeF_6$ requires Te, 23·9; F, 19·9; N, 9·7%]; *-chloro-*, stable yellow crystals, m. p. 145° [Found: Te, 18·2; Cl, 31·4; N, 8·0

[3] Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen, London, 1954, p. 294.

$(C_7H_7SCN_2H_5)_2TeCl_6$ requires Te, 18·9; Cl, 31·6; N, 8·3%]; *-bromo-*, stable orange needles, m. p. 158° [Found: Te, 14·0; Br, 51·9; N, 6·3. $(C_7H_7SCN_2H_5)_2TeBr_6$ requires Te, 13·5; Br, 51·1; N, 5·9%]. The hexaiodotellurite could not be prepared, a brown oil being obtained.

On dissolution of the hexafluorotellurite in hot hydrochloric acid and cooling the hexachlorotellurite was obtained. Hot hydrobromic acid converts either the fluoro- or the chloro-analogue into the hexabromotellurite.

Dithiuronium hexahalogenotellurites and their double salts with thiuronium chloride, and di-*S*-benzylthiuronium hexahalogenotellurites, do not effervesce with nitric acid, are insoluble in the common organic solvents, and are rapidly hydrolysed by water forming a precipitate of tellurous acid suspended in a solution of the corresponding halogen acid.

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CHEMISTRY DEPARTMENT, KING'S COLLEGE,
NEWCASTLE UPON TYNE. [*Received, April 25th,* 1958.]

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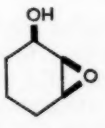
672. *Aspects of Stereochemistry. Part X.* The Preparation and Hydration of a Ditertiary Vicinal Epoxide of the Decalin Series.*

By H. B. HENBEST, MICHAEL SMITH, and A. THOMAS.

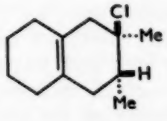
Acid-catalysed hydration of the bicyclic ditertiary epoxide (V) gave a mixture of the *trans*-diaxial diol (71%) and the *trans*-diequatorial diol (23%), the *cis*-diol (prepared separately) not being detected.

Nomenclature.—As a result of consultation with the Editors, whose assistance is gratefully acknowledged, the following proposals for the consistent naming of variously substituted *racemic* alicyclic compounds are made and used in this and later papers:

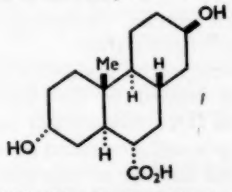
1. Racemic composition to be designated by the prefix (±).
2. General numbering to follow established rules (cf. Editorial Nomenclature Reports).
3. Relative configurations to be expressed as α or β (or ξ if unknown) for all groups, the reference position (arbitrarily designated as β) being chosen in the following descending order of preference: (*a*) a single group or atom other than hydrogen at the lowest-numbered position, (*b*) of two dissimilar groups at the lowest-numbered position that one which is named as a suffix, (*c*) of two dissimilar groups at the lowest-numbered position both named a prefixes, that which is named first in alphabetical order, and (*d*) if identical groups are present at the lowest-numbered position, apply (*a*)—(*c*) to the next higher-numbered positions until a decision can be reached. Three examples are as shown.



(±)-2β : 3β-Epoxy-*cyclo*hexan-1β-ol (reference group : 1β-OH).



(±)-2β-Chloro-2α : 3α-dimethyl-Δ⁵-octalin (reference group : 2β-Cl).



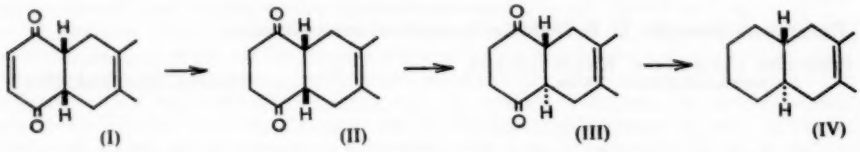
(±)-11β : 12α : 14α-Tetradecahydro-2β : 7α-dihydroxy-13β-methylphenanthrene-9α-carboxylic acid (reference group : 2β).

As illustrated by these examples, in the representation of racemic compounds by formulæ, the enantiomer can be chosen which conforms to its racemic name when heavy lines indicate " β " and dotted lines " α "-substituents. However, in a series of reactions rigid application of this could sometimes lead (in the formulæ) to the inversion of the other

* Part IX, *J.*, 1957, 4765.

centres of asymmetry not involved in particular reactions: in such cases it may be more convenient to keep to one enantiomeric series of formulæ throughout. Thus the diol (VIII; below) is written as shown in order to show its relation with the epoxide (V) from which it is prepared, although for nomenclatural purposes the positions 2 and 3 are reversed in the two racemic compounds. Previous uses of αβ-nomenclature in cyclic systems may be noted.[1-4]

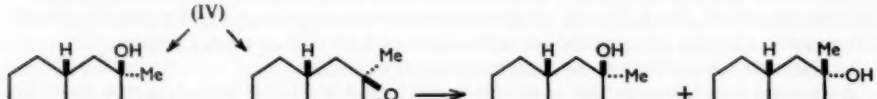
THE purpose of the present investigation was to prepare a group of three isomeric cyclic ditertiary diols of defined conformation (*i.e.*, VI, VII, and VIII) with a view to under-



(I) (II) (III) (IV)

standing better the stereochemical requirements of the glycol fission reaction. *En route* to these diols the stereochemical course of the hydration of the simple bicyclic ditertiary epoxide (V) could be examined.

The precursor of the diols was the bicyclic olefin (IV) which was synthesised in the following way. Reduction of the Diels–Alder adduct (I) with zinc in aqueous acetic acid yielded the *cis*-ring diketone (II). This, on suitable treatment with alkali, was converted into its higher-melting *trans*-isomer (III). Wolff–Kishner reduction then gave the desired olefin (IV), from which the epoxide (V) and the *cis*-diol (VI) were readily obtained.



(VI) (V) (VII) (VIII)

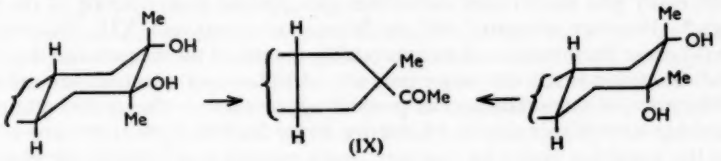
Hydration of the epoxide (V) in aqueous acetone solution with sulphuric acid as catalyst and chromatography of the products gave two crystalline diols which, being different from the *cis*-diol (VI), could be assigned *trans*-configurations. The higher-melting isomer of the pair has been assigned the diaxial diol structure (VII) as (*a*) it is formed in larger amount (71% as opposed to 23% of the diequatorial diol, VIII), (*b*) it is more easily eluted from an alumina chromatogram, and (*c*) it is the most resistant of the three isomers to pinacolic dehydration.

Owing to the possibility of ring inversion there are in the monocyclic series only two isomers related to the diols (VI—VIII). Both of these give 1-acetyl-1-methyl*cyclo*pentane (IX; monocyclic) on treatment with acid, but significantly the *trans*-diol, where both hydroxyl groups can be equatorial, reacts the more rapidly.[5,6] Clearly, these pinacolic reactions leading to ring contraction depend on the migration of an annular C–C bond which is parallel to the equatorial C–OH bond undergoing acid-induced ionisation. Observations with the bicyclic diols have amplified these previous findings. The diaxial diol was largely unchanged under conditions which caused almost sole production of a ketone

[1] Fieser, *J. Amer. Chem. Soc.*, 1950, **72**, 623.
[2] Fodor and Nádor, *J.*, 1953, 721.
[3] Cookson, *J.*, 1954, 282.
[4] Lemieux, Kullnig, and Moir, *J. Amer. Chem. Soc.*, 1958, **80**, 2237.
[5] Bartlett, quoted by Klyne in "Progress in Stereochemistry," Butterworths Scientific Publ., London, 1954, p. 73.
[6] Meerwein, *Annalen*, 1939, **542**, 123.

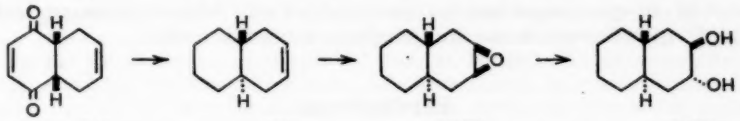
from the other two isomers containing one or two equatorial hydroxyl groups. This ketone (formulated as IX; bicyclic) was characterised as its 2 : 4-dinitrophenylhydrazone, the overall yield of derivative being higher from the diequatorial than from the mono-equatorial diol.

In order to discuss the hydration of the tetrasubstituted epoxide (V) it was desirable to determine the yield of diaxial diol to be expected as the main product from hydration



(IX)

of the related disubstituted epoxide (XII). This epoxide was prepared from the octalin (XI), obtained in turn from the Diels–Alder adduct (X) by a route analogous to that used for the tetrasubstituted olefin (IV); however, the yields in the *cis* ⟶ *trans* isomerisation and the Wolff–Kishner reduction steps were lower. Acid-catalysed hydration of



(X) (XI) (XII) (XIII)

disubstituted epoxide (XII) gave a diol (90%) to which the diaxial structure (XIII) may be assigned by analogy with similar reactions in the steroid series. The *cis*- and the *trans*-diequatorial isomers of (XIII) were not detected on alumina chromatography of the total hydration product. [A product, clearly the diaxial diol (XIII), has been obtained [7] by hydroxylation of the olefin (XI) prepared by a different route starting from β-decalol. Ali and Owen [8] have recently prepared the olefin by this route and have fully characterised the three possible racemic diols derivable by direct or indirect hydroxylation. Melting-point comparisons confirmed that the *cis*- and the *trans*-diaxial diols prepared from our olefin and from Ali and Owen's olefin were identical.]

Electronic and steric effects influence the direction of opening of unsymmetrically substituted epoxides.[9] The general trends are that strongly nucleophilic reagents tend to attack the less substituted carbon atom whereas electrophilic agents promote Markownikow ring opening, an anion becoming linked to the more alkylated carbon atom. The latter type of reaction receives a simple explanation in terms of carbonium-ion intermediates, and support comes from recent studies on the kinetics of the acid-catalysed hydration of epoxides where it was concluded that, as the reaction velocity could be related to Hammett's acidity function H_0, carbonium-ion formation from the epoxide conjugate acid represents the rate-determining step.[10]

When, however, the stereochemistry of epoxide ring opening under acidic conditions is considered it seems unlikely that " carbonium-ion formation " is the whole story. Thus disecondary epoxy*cyclo*alkanes yield *trans*-products with little or none of the *cis*-products that could equally well be formed *via* simple carbonium ions. Moreover disecondary epoxy*cyclo*hexanes, *e.g.*, (XII), yield *trans*-diaxial compounds, the specificity suggesting that the solvent, as a nucleophil, is intimately concerned in the reactions, which may be

[7] Hückel and Naab, *Annalen*, 1933, **502**, 151.
[8] Ali and Owen, *J.*, 1958, 2119.
[9] For a recent discussion see Eliel in " Steric Effects in Organic Chemistry," Wiley & Sons, New York, 1956.
[10] Pritchard and Long, *J. Amer. Chem. Soc.*, 1956, **78**, 2663, 2667, 6008.

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regarded as displacement processes where the reacting groups take up a linear arrangement most readily when a diaxial compound is being formed. Further evidence indicating that nucleophilic solvent participation is not excluded by dependence of rate on H_0 comes from studies on the acid-catalysed racemisation of active butan-2-ol in $H_2{}^{18}O$ where although log k and H_0 are related linearly, every hydroxyl exchange is accompanied by inversion.[11]

Even in the tetrasubstituted epoxide (V) where the presence of tertiary carbon atoms could more easily give rise to open carbonium ions, specific *trans*-opening of the ring still takes place.* However, compared with the disecondary compound (XII), the extra methyl groups in (V) cause the formation of an appreciable amount of the diequatorial diol although the diaxial compound is still the major product. Displacement reactions are still involved and the formation of some diequatorial product appears due to the methyl groups' somewhat inhibiting solvent approach and favouring larger fractional positive charges on either carbon in the transition states for reaction; more random ring opening therefore occurs. It is hoped that further work will help to clarify the situation.

In discussing the formation of diequatorial products in six-membered ring systems it may be noted that small amounts of these isomers frequently accompany diaxial products in reactions of ammonia with some benzylidenehexoses;[14] *cis*-products have again not been detected. The most extreme example of equatorial ring opening appears to be the reduction of 5β : 6β-epoxycoprostane to coprostan-5β-ol with lithium aluminium hydride in 60% yield;[15] special steric factors are thought to cause this result.

Experimental

M. p.s were determined on a Kofler hot stage. Alumina (P. Spence, Grade H) was deactivated with dilute acetic acid.[16] Light petroleum refers to the fraction, b. p. 60—80°.

6 : 7-*Dimethyl*-Δ^6-cis-*octalin*-1 : 4-*dione* (II).—Finely powdered 6 : 7-dimethyl-$\Delta^{2:6}$-*cis*-hexalin-1 : 4-dione (I) (50 g.) was dissolved in acetic acid at 50°, and immediately poured into a vigorously stirred suspension of zinc dust (50 g.) in water (200 c.c.) also at 50°. Stirring was continued for 2 min., during which the yellow colour disappeared and the temperature rose to 75°. The hot mixture was filtered, and water (1 l.) was added to the filtrate, which was cooled to 0°. The product (44·5 g., 88%), m. p. 120°, crystallised as needles. An analytical sample of the cis-*diketone* had m. p. 119—120° (from light petroleum) (Found: C, 74·95; H, 8·3. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·4%).

(±)-6 : 7-*Dimethyl*-Δ^6-9β : 10α-*octalin*-1 : 4-*dione* (III).—N-Sodium hydroxide (280 c.c.) was added during 10 min. to a vigorously stirred solution of the *cis*-diketone (50 g.) in dioxan (250 c.c.) at 80° under nitrogen. The mixture was neutralised with hydrochloric acid, diluted with water (1 l.), and cooled to 0°. The product (45·5 g., 91%) had m. p. 168—169°. The pure trans-*diketone* had m. p. 169° (change of form at 120°) (from light petroleum) (Found: C, 75·2; H, 8·45%).

(±)-2 : 3-*Dimethyl*-Δ^2-9β : 10α-*octalin* (IV).—A solution of the *trans*-diketone (129 g.) and 90% hydrazine hydrate (130 c.c.) in diethylene glycol (1250 c.c.) was heated under reflux for 1 hr. Potassium hydroxide (130 g.) was added in portions during 20 min., and then the mixture was distilled until the vapour temperature reached 180°. The mixture was heated under reflux for 5 hr. (two layers formed). Water and pentane were added to the cooled mixture. Distillation of the product from the pentane extract yielded the *olefin* (78 g., 70%), b. p. 61°/0·3 mm., n_D^{21} 1·4926 (Found: C, 87·85; H, 12·25. $C_{12}H_{20}$ requires C, 87·8; H, 12·2%).

* As far as the possible formation of *cis*-diol is concerned, hydration of the monocyclic 1 : 2-epoxy-1 : 2-dimethyl*cyclo*hexane could equally well be studied. This reaction has been reported to give the *trans*-diol (80%).[12] The formation of cholestane-3α : 5α-diol from the acid-catalysed hydration of 3α : 5α-epoxycholestane shows that a *cis*-diol can be produced from 1 : 3-epoxide probably *via* an "open carbonium ion."[13]

[11] Bunton, Konasiewicz, and Llewellyn, *J.*, 1955, 604.
[12] Nametkin and Delektorsky, *Ber.*, 1924, **57**, 583.
[13] Clayton, Henbest, and Smith, *J.*, 1957, 1982.
[14] For references see Overend and Vaughan, *Chem. and Ind.*, 1955, 995.
[15] Hallsworth and Henbest, *J.*, 1957, 4604.
[16] Farrar, Hamlet, Henbest, and Jones, *J.*, 1952, 2657.

XUM

(±)-2α : 3α-*Dimethyl*-9β : 10α-*decalin*-2β : 3β-*diol* (VI).—A solution of the olefin (0·63 g.) and osmium tetroxide (1 g.) in ether (50 c.c.) was kept at 20° for 48 hr. The ether was evaporated, and the residue was dissolved in tetrahydrofuran (50 c.c.) and shaken with a solution of mannitol (10 g.) and potassium hydroxide (10 g.) in water (50 c.c.) for 8 hr. The product (isolated with ether) was dissolved in light petroleum and adsorbed on deactivated alumina (10 g.). Elution with light petroleum gave some oil. Elution with ether–light petroleum (1 : 1) gave the cis-*diol* (0·4 g.), m. p. 83—89° (from pentane) (Found: C, 72·55; H, 10·85. $C_{12}H_{22}O_2$ requires C, 72·7; H, 11·2%).

(±)-2β : 3β-*Epoxy*-2α : 3α-*dimethyl*-9β : 10α-*decalin* (V).—The olefin (25 g.) was added dropwise to a stirred 2N-ethereal solution of monoperphthalic acid (170 c.c.) maintained below 10°. The mixture was then kept at 20° for 1 hr., whereafter the phthalic acid was removed by filtration. The filtrate was washed with dilute alkali and dried. Distillation afforded the *epoxide* (24·2 g., 88%), b. p. 60·5°/0·2 mm., n_D^{19} 1·4776 (Found: C, 79·5; H, 11·1. $C_{12}H_{20}O$ requires C, 79·9; H, 11·2%).

Hydration of the Epoxide (V).—The epoxide (2·81 g.), acetone (5 c.c.), water (5 c.c.) and concentrated sulphuric acid (66 mg.) were shaken together at 20° for 1 hr. to give a homogeneous solution. This was kept at 20° for 23 hr., then the products were isolated with ether and chromatographed on deactivated alumina (250 g.). Elution with benzene–light petroleum gave unchanged epoxide (45 mg., 1·5%) (infrared evidence). Elution with benzene (1·6 l.) gave (±)-2α : 3α-*dimethyl*-9β : 10α-*decalin*-2β : 3α-*diol* (VII) (2·199 g., 71%), m. p. 119—121° (from light petroleum) (Found: C, 72·8; H, 10·9. Further elution with benzene (1·1 l.) and with ether (400 c.c.) afforded (±)-2α : 3β-*dimethyl*-9α : 10β-*decalin*-2β : 3α-*diol* (VIII) (0·701 g., 23%), m. p. 81—85° (from pentane) (Found: C, 72·5; H, 11·05%). Separate careful chromatography of an artificial mixture of the three diols gave a good separation, the *cis*-diol being eluted after the diaxial diol. The benzene eluate from chromatography of the product from the hydration experiment was collected in fractions, but a plot of fraction weight against number gave no evidence for the presence of the *cis*-diol. [A strong depression of m. p. (to 50—60°) was recorded on admixture of the *cis*- and the *trans*-diequatorial diol.] The infrared absorption of the total reaction product exhibited the bands of the two *trans*-diols; no extra bands due to an *iso*propylidene compound were present. The *cis*-diol was recovered unchanged (96%) on treatment with the acetone–sulphuric acid mixture used in the hydration experiment (therefore no *iso*propylidene derivative was formed).

Pinacolic Dehydration of the Diols.—Each diol (50 mg.) in water (12·5 c.c.), dioxan (5 c.c.), and concentrated sulphuric acid (0·25 c.c.) was heated under reflux for 15 hr. The products were isolated with ether and examined by infrared spectroscopy. The diaxial diol was about 80% unchanged, as there was only a small carbonyl band near 1700 cm.$^{-1}$. The products from the other two diols showed no hydroxyl bands but each had a strong carbonyl band at 1700 cm.$^{-1}$ and another medium band at 1355 cm.$^{-1}$ (*C*-acetyl groups, *e.g.*, 21-methyl-20-oxo-steroids, give a band at 1357 cm.$^{-1}$). The products from the *cis*-diol and from the diequatorial diol both gave the same 2 : 4-*dinitrophenylhydrazone* (70 and 88% yields respectively), m. p. 128—129°, of the ketone (IX) (Found: C, 59·65; H, 6·8; N, 15·2. $C_{18}H_{24}O_4N_4$ requires C, 60·0; H, 6·7; N, 15·55%).

$\Delta^{2:6}$-cis-*Hexalin*-1 : 4-*dione* (X).—*p*-Benzoquinone (100 g.) and butadiene (100 g.) in benzene (1 l.) were kept at 20° for 2 weeks. The solution was filtered, the solvent removed, and the residue recrystallised from light petroleum–benzene to give the diketone (141 g., 94%), m. p. 57° (lit., m. p. 58°).

Δ^{6}-cis-*Octalin*-1 : 4-*dione*.—Finely powdered $\Delta^{2:6}$-*cis*-hexalin-1 : 4-dione (100 g.) was dissolved in acetic acid (200 c.c.) at 50° and poured into a vigorously stirred suspension of zinc (125 g.) in water (250 c.c.) at 50°. Stirring was continued for 2 min., during which the yellow colour disappeared and the temperature rose to *ca.* 75°. The hot mixture was filtered, and water (1·5 l.) was added to the filtrate, which was kept at 0° overnight. The product (70 g., 70%), m. p. 90—108°, was dried and recrystallised from light petroleum to give the diketone, m. p. 105—108° (lit., m. p. 108°).

(±)Δ^{6}-9β : 10α-*Octalin*-1 : 4-*dione*.—Δ^{6}-*cis*-Octalin-1 : 4-dione (100 g.) was dissolved in dioxan (400 c.c.) at 80° and N-sodium hydroxide solution (648 c.c.) was added to the vigorously stirred solution under nitrogen during 10 min. Some *trans*-compound (2 g.; obtained in smaller-scale experiments) and water (300 c.c.) were added, and the solution was neutralised with 1·3N-hydrochloric acid. More water (1 l.) was added and the solution kept at 0° overnight to

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give a product (20 g., 20%), m. p. 150—160°. The pure trans-*diketone* had m. p. 157—160° (from light petroleum) (Found: C, 73·05; H, 7·0. $C_{10}H_{12}O_2$ requires C, 73·15; H, 7·35%).

(±)Δ^2-9β : 10α-*Octalin* (XI).—The *trans*-diketone (16 g.) and hydrazine hydrate (21 c.c., 85%) in diethylene glycol (160 c.c.) were refluxed for 1 hr. The excess of hydrazine hydrate and water was distilled off, the vapour temperature reaching 180°. Potassium hydroxide (19·5 g.) was added in portions during 5 min., and the mixture was refluxed for 5 hr. The cold mixture was diluted with water and extracted with light petroleum (1 l.), and the extract percolated through alumina (70 g.). Removal of the solvent at atmospheric pressure left a product which on distillation at a bath-temperature of 110°/15 mm. gave the olefin (5·06 g., 38%), n_D^{20} 1·4865 (Found: C, 88·30; H, 11·6. Calc. for $C_{10}H_{16}$: C, 88·15; H, 11·85%).

(±)9β : 10α-*Decalin*-2β : 3β-*diol*.—The olefin (0·52 g.) and osmium tetroxide (1 g.) in ether (50 c.c.) were kept at room temperature for 48 hr. The ether was evaporated, and the residue dissolved in dioxan (50 c.c.) and shaken with a solution of mannitol (10 g.) and potassium hydroxide (10 g.) in water (50 c.c.) for 8 hr. The solid product (isolated with ether) was dissolved in benzene and adsorbed on deactivated alumina (20 g.). Elution with benzene gave a trace of oil. Elution with ether (300 c.c.) gave the *cis*-diol (0·37 g., 57%), m. p. 140—141° (from benzene–light petroleum) (lit.,[17] m. p. 141°).

(±)2 : 3-*Epoxy*-9β : 10α-*decalin* (XII).—The olefin (1·5 g.) in ether (5 c.c.) was added to a stirred solution of monoperphthalic acid (0·356M; 42 c.c.) at 0°. The mixture was kept at 20° for 1·5 hr., washed with dilute alkali, then water, and dried ($MgSO_4$). Distillation afforded the *epoxide* (1·17 g., 70%), b. p. 95°/12 mm., n_D^{24} 1·4872 (Found: C, 78·65; H, 10·7. $C_{10}H_{16}O$ requires C, 78·9; H, 10·6%).

Hydration of the Epoxide.—The epoxide (0·628 g.), dioxan (6 c.c.), water (4 c.c.), and concentrated sulphuric acid (57 mg.) were shaken at room temperature for 24 hr. The solid product (isolated with ether) was chromatographed on deactivated alumina (65 g.). Elution with benzene–light petroleum gave unchanged epoxide (16 mg., 2%) (identified by formation of further diol, m. p. 161—163°, on acid hydrolysis). Elution with benzene–ether (1 : 1) (680 c.c.) gave (±)9β : 10α-decalin-2β : 3α-diol (XIII) (0·63 g., 90%), m. p. 163—164° (from benzene–light petroleum) (lit.,[7] m. p. 163°). The m. p.s of this diol and of the *cis*-diol were undepressed on admixture with authentic samples kindly provided by Dr. L. N. Owen (Imperial College, London).

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The University, Manchester, 13.
King's College, Strand, London, W.C.2.
Queen's University, Belfast.

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[17] Ganapathi, *Ber.*, 1939, **72**, 1381.

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673. *The Chemotherapy of Schistosomiasis. Part I. Derivatives and Analogues of αω-Di-(p-aminophenoxy)alkanes.*

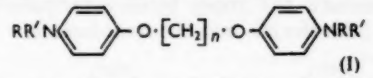
By J. N. Ashley, R. F. Collins, M. Davis, and N. E. Sirett.

A series of αω-di-(*p*-aminophenoxy)alkanes of the general formula (I; R = R′ = H) has been prepared and tested against *Schistosoma mansoni* infections in mice. Modifications of this fundamental molecular type which have been explored, in an attempt to establish a structure–activity relationship, include substitution in the amino-groups, the rings, and the central chain, and replacement of the central chain by other linkages. Many of the compounds exhibit high schistosomicidal activity.

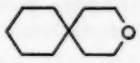
Schistosomiasis is one of the greatest unsolved problems in tropical medicine, and an inexpensive and safe drug which can be administered orally is an outstanding need. An extensive programme of work has been pursued in these laboratories during the last few years in the search for such a drug and several hundred compounds have been synthesised, and screened by our biological colleagues against *Schistosoma mansoni*.

Schistosomicidal activity was discovered early in 1952 in a series of aromatic diamines

of the general formula (I; R = R′ = H; *n* = 3—9), many of which had been prepared some ten years earlier for another purpose.



(I)



(II)

A preliminary announcement [1] of this work was made after the disclosure in the patent literature that the same series had been investigated independently by Raison and Standen.[2] Full details of the biological tests and the results obtained are being recorded elsewhere.[3] In this paper, the first of a series dealing mainly with compounds containing the *p*-aminophenoxyalkyl group, we shall describe the preparation of some primary, secondary, and tertiary amines of type (I) together with derivatives and analogues in which, for example, the central chain has been modified or further substituents introduced into the rings. Most of the simpler compounds have already been mentioned in patent specifications.[4,5] Since they were generally obtained by conventional methods, in reasonable yields, and with satisfactory analyses, and their melting points are recorded in these patents, further preparative details, solvents for recrystallisation, analytical figures, etc., have in most cases been omitted from this paper.

The di(nitrophenoxy)alkanes were obtained by condensation of potassium nitrophenoxide with the appropriate dibromide. Compounds not previously reported are listed in Table 1. Reduction of the dinitro-compounds to the diamines (Table 2) was effected either catalytically or by sodium sulphide. An alternative route also employed in some instances was the condensation of the appropriate acetamidophenol with the dibromide, followed by hydrolysis of the acetyl groups. The unsymmetrical dinitro-compounds were prepared by reaction of 1 : 5-dibromopentane with a limited amount of potassium *p*-nitrophenoxide to give 5-*p*-nitrophenoxypentyl bromide, followed by further reaction with potassium *o*- or *m*-nitrophenoxide.

At one time a substantial amount of 1 : 8-dibromo-octane was needed and its preparation from the readily available 1 : 4-dibromobutane was undertaken. Of the methods described in the literature for the preparation of αω-polymethylene dihalides, the Wurtz reaction has the advantage of few stages and is stated to give good overall yields, although the best practical details for the synthesis of 1 : 8-dibromo-octane have not been fully recorded.[6] We investigated this method and obtained 1 : 8-dibromo-octane from 1 : 4-dibromobutane in about 30% overall yield.

In Table 3 are listed compounds in which the simple polymethylene chain of the parent compound has been replaced by branched chains, benzene, or *cyclo*hexane rings, etc. 1 : 5-Dibromo-3-methylpentane has previously been made by treating 1-benzoyl-4-methylpiperidine with phosphorus tribromide.[7] It was more conveniently prepared from 2-ethoxy-3 : 4-dihydro-4-methylpyran by fission with acid to 3-methylglutaraldehyde, catalytic reduction to the glycol, and treatment with hydrobromic acid.[8] The glycol has previously been obtained from diethyl 3-methylglutarate by reduction over copper chromite.[9] When 1 : 1-di-(2-hydroxyethyl)*cyclo*hexane, prepared by reduction of *cyclo*hexylidenediacetic acid, was treated with 50% hydrobromic acid, the dibromide produced was always accompanied by appreciable amounts of the tetrahydropyran (II).

[1] Collins, Davis, and Hill, *Chem. and Ind.*, 1954, 1072.
[2] Raison and Standen, *Trans. Roy. Soc. Trop. Med. Hyg.*, 1954, **48**, 446; *Brit. J. Pharmacol.*, 1955, **10**, 191; Caldwell and Standen, *ibid.*, 1956, **11**, 367; Standen and Walls, *ibid.*, p. 375; Gorvin, Raison, Solomon, Standen, and Walls, *ibid.*, 1957, **12**, 329; Goodwin, Richards, and Udall, *ibid.*, p. 468.
[3] Hill, *Ann. Trop. Med. Parasitol.*, 1956, **50**, 39; Edge, Mason, Wien, and Ashton, *Nature*, 1956, **178**, 806; Collins, Davis, Edge, and Hill, *Brit. J. Pharmacol.*, in the press.
[4] May and Baker Ltd., B.P. 761,888; 768,144.
[5] The Wellcome Foundation Ltd., B.P. 749,907; 749,923; 758,382; 770,410; 770,411; 775,478.
[6] von Braun, *Ber.*, 1909, **42**, 4541; von Braun and Kamp, *Ber.*, 1937, **70**, 973; Ziegler and Weber, *ibid.*, p. 1275; Ziegler, Weber, and Gellert, *Ber.*, 1942, **75**, 1715.
[7] Leonard and Wicks, *J. Amer. Chem. Soc.*, 1946, **68**, 2402.
[8] Longley and Emerson, *ibid.*, 1950, **75**, 3080; cf. Smith, Norton, and Ballard, *ibid.*, 1951, **73**, 5267.
[9] Wojcik and Adkins, *ibid.*, 1933, **55**, 4943.

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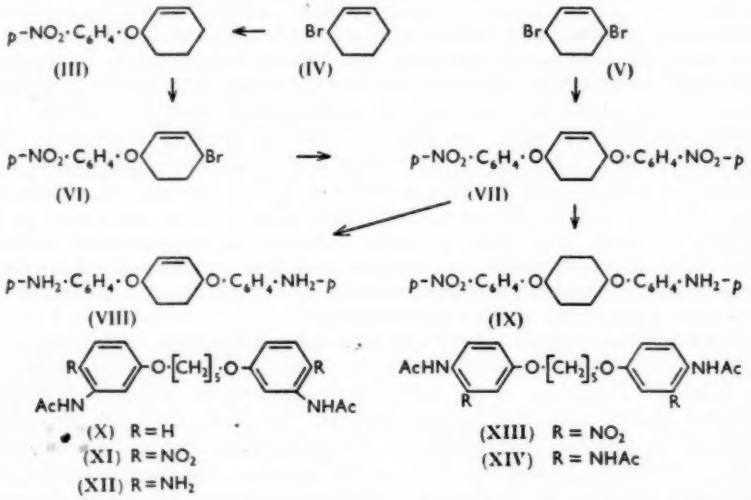
For the preparation of 1 : 4-di-(*p*-aminophenoxy)but-2-yne condensation of 1 : 4-dibromobut-2-yne [10] with *p*-acetamidophenol, followed by hydrolysis of the product, proved satisfactory. Attempts partially to reduce the triple bond over palladium–calcium carbonate led to a mixture containing both the *cis*- and the *trans*-butene. The pure *cis*-



and *trans*-isomers were obtained by condensation of the appropriate dibromides with potassium *p*-nitrophenoxide in dry acetone to give, respectively, *cis*- and *trans*-1 : 4-di-(*p*-nitrophenoxy)but-2-ene, which were reduced by iron and acetic acid to the corresponding *cis*- and *trans*-1 : 4-di-(*p*-aminophenoxy)but-2-ene. Both amines were reduced catalytically to the known 1 : 4-di-(*p*-aminophenoxy)butane, thus proving that the 1 : 4-dibromobut-2-ene used had not isomerised to 1 : 2-dibromobut-3-ene during the reaction.

The synthesis of the *cyclo*hexene and *cyclo*hexane analogues was then investigated. 3 : 6-Dibromo*cyclo*hexene [11] (V) resembles 1 : 4-dibromobut-2-ene in undergoing allylic rearrangement under certain conditions. Thus, with sodium hydrogen carbonate it is reported [12] to be hydrolysed to a mixture of *cis*- and *trans*-3 : 4-dihydroxy*cyclo*hexene and *cis*-3 : 6-dihydroxy*cyclo*hexene. However, concurrent work described above established that both *cis*- and *trans*-1 : 4-dibromobut-2-ene reacted normally without rearrangement. 3 : 6-Dibromo*cyclo*hexene (V) was therefore treated with potassium *p*-nitrophenoxide in the usual manner; it reacted rapidly and completely to give 3 : 6-di-(*p*-nitrophenoxy)-*cyclo*hexene (VII) in good yield. This compound was also obtained by the following route (explored primarily for the synthesis of other compounds to be described in a later paper). Treatment of *cyclo*hexene with *N*-bromosuccinimide gave the known 3-bromo*cyclo*hexene [13] which with potassium *p*-nitrophenoxide formed 3-*p*-nitrophenoxy*cyclo*hexene (III) in high yield. Further bromination with *N*-bromosuccinimide gave 3-bromo-6-*p*-nitrophenoxy-*cyclo*hexene (VI) which was not isolated but was condensed *in situ* with a further quantity of potassium *p*-nitrophenoxide to yield the diphenoxy-compound (VII). *N*-Bromosuccinimide is normally a specific reagent for a methylene group α to a double bond and it attacks an unsubstituted methylene group [*i.e.*, the 6-position of (III)] more readily than a substituted one (*i.e.*, the 3-position) (cf. Djerassi [14]).

[10] Johnson, *J.*, 1946, 1009.
[11] Farmer and Scott, *J.*, 1929, 172.
[12] Bedos and Ruyer, *Compt. rend.*, 1937, **204**, 1380.
[13] Ziegler, Spaeth, Schaaf, Schumann, and Winkelmann, *Annalen*, 1942, **551**, 80.
[14] Djerassi, *Chem. Rev.*, 1948, **43**, 273.

With iron and acetic acid only the nitro-groups of compound (VII) were reduced, giving 3 : 6-di-(*p*-aminophenoxy)*cyclo*hexene (VIII), which was further reduced over platinum oxide to the saturated base (IX). The nitro-compound could be reduced directly to the saturated base over palladium–calcium carbonate, but not over platinum oxide, the mixture becoming dark and only a trace of the required base being isolated. Probably hydrogenolysis of the ether linkage occurred. 1 : 4-Di-(*p*-aminophenoxy)*cyclo*hexane (IX) was also prepared more directly from *trans*-1 : 4-ditoluene-*p*-sulphonyloxy*cyclo*hexane:[15] condensation with potassium *p*-nitrophenoxide in 2-ethoxyethanol (no reaction occurred in acetone) gave a low yield of 1 : 4-di-(*p*-nitrophenoxy)*cyclo*hexane (together with unidentified unsaturated products), which was reduced over platinum oxide to the diamine (IX). Final confirmation that the unsaturated intermediates employed had not undergone rearrangement was obtained by treatment of this amine (IX) with hydrobromic acid, *trans*-1 : 4-dibromo*cyclo*hexane being obtained.

The nuclear-substituted compounds shown in Tables 4 and 5 were mostly obtained by conventional methods. For the preparation of 1 : 5-di-(3-acetamido-4-aminophenoxy)-pentane (XII), the nitration of 1 : 5-di-(*m*-acetamidophenoxy)pentane (X) was examined, as previous work on the nitration of *m*-acetamido-anisole and -phenetole has shown that the 3-acetamido-4-nitrophenyl ether is the principal product.[16] The orientation of the product, 1 : 5-di-(3-acetamido-4-nitrophenoxy)pentane (XI), was confirmed by catalytic reduction to compound (XII) and acetylation, which gave 1 : 5-di-(3 : 4-bisacetamido-phenoxy)pentane (XIV) identical with a specimen prepared in a like manner from the isomeric 1 : 5-di-(4-acetamido-3-nitrophenoxy)pentane (XIII).

Many different methods were employed to make the *N*-substituted amines, most of which are described in the relevant patents.[4,5] The general procedures are outlined here with particular reference to derivatives of 1 : 5-di-(*p*-aminophenoxy)pentane (I; $n = 5$; R = R′ = H). The *NN*′-dimethyl derivatives (I; R = Me, R′ = H) were formed when *p*-(*N*-methylacetamido)phenol was condensed with the dibromoalkane and the acetyl group then removed by hydrolysis. Alkylation of the primary diamines with methyl iodide gave the bis-quaternary iodides, which on pyrolysis yielded the *NNN*′*N*′-tetramethyl derivatives (I; R = R′ = Me) in high yield. The *NNN*′*N*′-tetraethyl derivatives were similarly prepared, although the quaternary iodides were not obtained crystalline. Treatment of 1 : 5-di-(*p*-methylaminophenoxy)pentane (I; $n = 5$; R = Me, R′ = H) with an excess of ethyl bromide and pyrolysis of the product yielded the *NN*′-diethyl-*NN*′-dimethyl derivative (I; $n = 5$; R = Me, R′ = Et). Loss of ethyl iodide rather than methyl iodide from quaternary salts has been reported by Fahim and Fleifel.[17]

1 : 5-Di-(-*p*-ethylamino- and -*p*-*n*-propylaminophenoxy)pentane (I; $n = 5$; R = Et or Pr^n, R′ = H) were conveniently obtained by reduction of the diacetyl (I; $n = 5$; R = Ac, R′ = H) and dipropionyl derivatives (I; $n = 5$; R = COEt, R′ = H) of the primary diamines with lithium aluminium hydride. The diacetyl derivative was sparingly soluble in ether and tetrahydrofuran, and reduction was incomplete in these solvents, but proceeded satisfactorily in di-*n*-butyl ether. Propionylation and further reduction of the di-*n*-propyl compound afforded the tetra-*n*-propyl derivative. For the unsymmetrical *NN*-diethyl-*N*′*N*′-dimethyl derivative, *p*-(*N*-methylformamido)phenol was condensed with 5-*p*-nitrophenoxypentyl bromide to yield 1-[*p*-(*N*-methylformamido)phenoxy]-5-*p*-nitrophenoxypentane, and the nitro-group of the product was reduced catalytically. Acetylation of the primary amine formed, followed by lithium aluminium hydride reduction, yielded the *N*′-ethyl-*NN*-dimethyl compound. This was again acetylated and reduced to 1-*p*-diethylaminophenoxy-5-*p*-dimethylaminophenoxypentane.

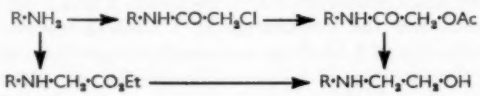
Condensation of *N*-acetyl-*p*-*iso*propylaminophenol with dibromopentane proceeded

[15] Owen and Robins, *J.*, 1949, 320.
[16] Reverdin and Widmer, *Ber.*, 1913, **46**, 4071; Reverdin and Lokietek, *Bull. Soc. chim. France*, 1916, **19**, 253.
[17] Fahim and Fleifel, *J.*, 1951, 2761.

XUM

readily giving 1 : 5-di-(*p-iso*propylaminophenoxy)pentane, but removal of the protecting group by hydrolysis proved unexpectedly difficult, and only a small amount of the base could be isolated. Condensation of 1 : 5-di-(*p*-aminophenoxy)pentane with acetone was next examined. Although the unstable *iso*propylidene derivative (I; $n = 5$; $RR' = :CMe_2$) could not be isolated, its reduction *in situ* in the presence of excess of acetone led to a reasonable overall yield of 1 : 5-di-(*p-iso*propylaminophenoxy)pentane (I; $n = 5$; $R = Pr^i$, $R' = H$).

1 : 5-Di-(*p*-hydroxyethylaminophenoxy)pentane (I; $n = 5$; $R = [CH_2]_2{\cdot}OH$, $R = H$) was prepared by two different routes from 1 : 5-di-(*p*-aminophenoxy)pentane (represented by $R{\cdot}NH_2$ in the annexed scheme). In both instances the final reduction was achieved with lithium aluminium hydride. The *NNN'N'*-tetra(hydroxethyl) derivatives (I; $R = R' = [CH_2]_2{\cdot}OH$) were made by boiling the primary amines with excess of aqueous ethylene chlorohydrin in the presence of calcium carbonate. The unsymmetrical *NN*-di-



(hydroxyethyl) derivative was obtained by condensation of 5-*p*-nitrophenoxypentyl bromide with *p*-di-(2-hydroxyethylamino)phenol, followed by reduction. After alkylation of 1 : 5-di-(*p*-aminophenoxy)pentane with 2-methoxyethyl chloride only the secondary amine, 1 : 5-di-(*p*-2-methoxyethylaminophenoxy)pentane (I; $n = 5$; $R = [CH_2]_2{\cdot}OMe$, $R' = H$), was isolated, albeit in low yield. Similar results attended the use of 2-diethylaminoethyl chloride.

1 : 5-Di-(*p*-pyrrolidinophenoxy)pentane was made both by direct condensation of 1 : 5-di-(*p*-aminophenoxy)pentane with 1 : 4-dibromobutane and by reduction of the corresponding disuccinimide with lithium aluminium hydride. The piperidino- and morpholino-analogues were obtained likewise from the diamine with 1 : 5-dibromopentane and di-(2-chloroethyl) ether respectively.

The *NN'*-dibenzyl derivative (I; $n = 5$; $R = CH_2Ph$, $R' = H$) was conveniently made by catalytic reduction of the dibenzylidene derivative of the primary diamine.

The best yields of 1 : 5-di-(*p*-pyrid-2-ylaminophenoxy)pentane were obtained by heating 2-bromopyridine and 1 : 5-di-(*p*-aminophenoxy)pentane with potassium carbonate and copper bronze at 170—180° for a limited period. 1 : 5-Di-(*p*-aminophenoxy)pentane with ammonium thiocyanate formed the thioureide which did not condense with chloroacetaldehyde (as the acetal). With chloroacetone, however, the 4-methylthiazole derivative was readily formed.

The formaldehyde bisulphite derivative (I; $n = 5$; $R = CH_2{\cdot}SO_3Na$, $R' = H$) of 1 : 5-di-(*p*-aminophenoxy)pentane was made by heating the base with an aqueous solution of sodium formaldehyde bisulphite.

In Table 6 are listed some diamines in which one or both oxygen linkages of the central dioxyalkane chain have been omitted or replaced by other linkages. The use of *p*-nitrothiophenol in place of *p*-nitrophenol led to the analogue containing two sulphur linkages. For the compound containing two NH linkages the condensation of *p*-aminoacetanilide with 1 : 3-dibromopropane was attempted, but afforded a mixture from which pure 1 : 3-di-(*p*-acetamidoanilino)propane could not be isolated. The alternative method of Veer [18] was therefore used, *p*-chloronitrobenzene being condensed with 1 : 3-diaminopropane, and the 1 : 3-di-(*p*-nitroanilino)propane formed reduced catalytically. The thiolsulphinate linkage —S—S(→O)— was first demonstrated in allicin.[19] Small, Bailey, and Cavallito [20] showed that thiolsulphinates were accessible by oxidation of the corresponding disulphide

[18] Veer, *Rec. Trav. chim.*, 1938, **57**, 989.
[19] Cavallito, Buck, and Suter, *J. Amer. Chem. Soc.*, 1944, **66**, 1952.
[20] Small, Bailey, and Cavallito, *ibid.*, 1947, **69**, 1710.

with perphthalic acid. Addition of the calculated quantity of perphthalic acid to a solution of di-(*p*-aminophenyl) disulphide in ether resulted in the precipitation of a salt (probably the phthalate of the thiolsulphinate). This was decomposed in sodium hydrogen carbonate or sodium acetate solution with liberation of the free thiolsulphinate, which possessed the characteristic properties of this linkage.[19] Thus, it reacted with cysteine in aqueous sodium hydrogen carbonate, its yellow colour being completely discharged in a few seconds. It was fairly stable towards dilute acids, but was decomposed by concentrated acids. For this reason it was not possible to prepare the same compound by acid hydrolysis of di-(*p*-acetamidophenyl) thiolsulphinate, earlier obtained from di-(*p*-acetamidophenyl) disulphide. Crystallisation of the thiolsulphinate required care, as in solvents it was unstable to heat. Acetone or aqueous pyridine gave the best recoveries, which even under favourable conditions did not exceed 40%.

Only the two lowest homologues of the series of αω-di-(*p*-aminophenyl)alkanes are described in the literature. Nitration of the diphenylalkanes is not readily controllable and gives even under mild conditions the 2 : 2′ : 4 : 4′-tetranitro-derivatives.[21] An alternative synthesis was therefore sought. Straus and Grindel [22] were able to reduce cinnamylideneacetophenone to 1 : 5-diphenylpentane over a palladium catalyst in acetone. We first established that this reduction was more rapid over Raney nickel in ethyl acetate and then applied the method to 1 : 5-di-(*p*-nitrophenyl)penta-2 : 4-dien-1-one, readily prepared from *p*-nitrocinnamaldehyde and *p*-nitroacetophenone. Reduction to 1 : 5-di-(*p*-aminophenyl)pentane proceeded smoothly.

Nitration of 5-phenylpentyl chloride at −10° is said to give substantially the *p*-nitro-derivative.[23] Nitration under identical conditions of 5-phenylpentyl bromide gave, however, a mixture of mono- and di-nitro-derivatives in which the latter predominated. It was characterised by condensation with *p*-nitrophenol and reduction of the trinitro-ether to the triamine. By carrying out the nitration of 5-phenylpentyl bromide at −50°, dinitration was minimised and the major product was the required 5-*p*-nitrophenylpentyl bromide. This could not be satisfactorily purified by distillation, but its orientation was confirmed by successive reaction with potassium acetate, hydrolysis, and oxidation with alkaline permanganate, only *p*-nitrobenzoic acid being then isolated. A small amount of *o*-nitrophenylpentyl bromide appeared to be simultaneously formed, since on condensation of the crude nitrated bromide with *p*-nitrophenol and chromatography of the product a small amount of an isomeric ether, probably 1-*p*-nitrophenoxy-5-*o*-nitrophenylpentane, was separated from the *p*-isomer.

Experimental

Light petroleum refers, unless otherwise stated, to the fraction of b. p. 40—60°.

Synthesis of 1 : 8-*Dibromo-octane by the Wurtz Reaction.*—1 : 4-Dibromobutane was prepared on a large scale by passage of dry hydrogen bromide into tetrahydrofuran. Fractionation of the high-boiling residue obtained after distillation of the dibromide gave di-(4-bromobutyl) ether (4%), b. p. 150—151°/13 mm. (Found: C, 33·3; H, 5·6; Br, 55·55. Calc. for $C_8H_{16}OBr_2$: C, 33·1; H, 5·6; Br, 55·5%) (lit.,[24] b. p. 142—147°/10 mm., 97—97·6°/1 mm.).

4-p-*Methoxyphenoxybutyl Bromide.*—Potassium hydroxide (67·5 g.) in methanol (200 ml.) was added to *p*-methoxyphenol (124 g.) in methanol (50 ml.), and the resulting solution was added during 1·5 hr. to 1 : 4-dibromobutane (432 g.) in acetone (400 ml.). The mixture was refluxed for 1 hr., concentrated, and diluted with water. The oil separating was taken up in ether, and the ethereal extract was filtered from 1 : 4-di-(*p*-methoxyphenoxy)butane (29 g.; m. p. 140—142°; Ziegler, Weber, and Gellert [6] give m. p. 142°), washed with dilute sodium hydroxide and water, dried, and distilled, giving recovered 1 : 4-dibromobutane (204 g.) and

[21] von Braun, Deutsch, and Koscielski, *Ber.*, 1913, **46**, 1524.
[22] Straus and Grindel, *Annalen*, 1924, **439**, 276.
[23] von Braun and Deutsch, *Ber.*, 1912, **45**, 2520.
[24] Ziegler and Hall, *Annalen*, 1937, **528**, 143; Müller and Vanc, *Ber.*, 1944, **77**, 669.

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4-*p*-methoxyphenoxybutyl bromide (200 g., 73% on dibromide used, 77% on *p*-methoxyphenol used), b. p. 180—193°/13 mm. The distillate had m. p. 42—44° (lit.,[25] m. p. 42—43°, b. p. 125—130°/1·5 mm.).

4-p-*Methoxyphenoxybutyl Iodide.*—A mixture of 4-*p*-methoxyphenoxybutyl bromide (1·545 kg.) and sodium iodide (1·26 kg.) in acetone (15 l.) was stirred and refluxed for 3 hr. The cooled solution was filtered, the filtrate was concentrated, and the residue was poured into water. The solid product was filtered off, ground, and washed with water, then dried over phosphoric oxide and silica gel, to yield 1·771 kg. (98·5%) of product, m. p. 54°. Recrystallisation from ether–light petroleum gave the *iodide* in plates, m. p. 55° (Found: I, 42·1. $C_{11}H_{15}O_2I$ requires I, 41·5%).

1 : 8-*Di*-(p-*methoxyphenoxy*)*octane.*—Sodium (100 g.) was powdered by rapidly stirring the molten metal under toluene. When cool, the toluene was decanted off and the sodium washed with dry ether, then suspended in dry ether (2 l.) and mechanically stirred. 4-*p*-Methoxyphenoxybutyl iodide (444 g.) was added and the stirred mixture was refluxed for 48 hr., then cautiously treated with ethanol and kept overnight. The product was filtered off, cautiously added to water, refiltered, washed, and dried. Recrystallisation of the solid (62—69%), m. p. 129—130°, from acetic acid gave plates, m. p. 131—132°. Ziegler, Weber, and Gellert [6] give m. p. 132°.

1 : 8-*Dibromo-octane.*—A mixture of 1 : 8-di-(*p*-methoxyphenoxy)octane (613 g.), phenol (450 g.), and 50% aqueous hydrobromic acid (1·5 l.) was stirred and refluxed overnight, then steam-distilled. The distillate was extracted with ether, and the extract was washed with dilute aqueous sodium hydroxide and water, dried, and evaporated. Distillation of the residue gave 1 : 8-dibromo-octane (324 g., 70%), b. p. 150—152°/16 mm.

TABLE 1. *Compounds* $NO_2 \cdot C_6H_4 \cdot O \cdot [CH_2]_n \cdot O \cdot C_6H_4 \cdot NO_2$.

Position of NO_2 groups	*n*	Yield (%)	M. p.	Formula	Found (%) N	Reqd. (%) N
2 : 2′	3	54	111—113°	$C_{15}H_{14}O_6N_2$	8·7	8·8
2 : 2′	5	30	84 [a]	$C_{17}H_{18}O_6N_2$	8·5	8·1
2 : 2′	8	47	107	$C_{20}H_{24}O_6N_2$	7·4	7·2
3 : 3′	3	50	122—124	$C_{15}H_{14}O_6N_2$	8·95	8·8
3 : 3′	5	33	90	$C_{17}H_{18}O_6N_2$	8·1	8·1
4 : 2′	5	73	67—68	$C_{17}H_{18}O_6N_2$	8·2	8·1
4 : 3′	5	91	63—65	$C_{17}H_{18}O_6N_2$	8·3	8·1
4 : 4′	8	67	118—120	$C_{20}H_{24}O_6N_2$	7·1	7·2
4 : 4′	9	44	90—92 [a]	$C_{21}H_{26}O_6N_2$	7·1	7·0
4 : 4′	10	25	86	$C_{22}H_{28}O_6N_2$	6·55	6·7
4 : 4′	12	60	81—83	$C_{24}H_{32}O_6N_2$	6·5	6·3

[a] First prepared by Mr. S. S. Berg.

5-p-*Nitrophenoxypentyl Bromide.*—This was prepared by refluxing potassium *p*-nitrophenoxide (3·8 kg.) and 1 : 5-dibromopentane (9·9 kg.) in acetone (9 l.) overnight; 3·41 kg. (55%) of the bromide, containing a small amount of 1 : 5-di-(*p*-nitrophenoxy)pentane, were obtained. Pure 5-*p*-nitrophenoxypentyl bromide, obtained by chromatography or by distillation of the crude product (in small batches), had m. p. 34·5—35·5°, b. p. 160°/0·2 mm. (Found: N, 4·8; Br, 27·35. Calc. for $C_{11}H_{14}O_3NBr$: N, 4·85; Br, 27·8%) (lit.,[5] m. p. 33—34°). Fractionation of the dibromopentane recovered from this experiment gave a small amount of low-boiling material. After re-fractionation it had b. p. 34—38°/18 mm. and appeared to be 5-*bromopentyl pent-4-enyl ether* (Found: C, 51·8; H, 8·0; Br, 33·95. $C_{10}H_{19}OBr$ requires C, 51·1; H, 8·15; Br, 33·95%).

Similarly prepared were 3-p-*nitrophenoxypropyl bromide* (49%), m. p. 51° (Found: Br, 30·7. $C_9H_{10}O_3NBr$ requires Br, 30·7%), and 4-p-*nitrophenoxybutyl bromide* (37%), m. p. 37—40° (Found: N, 4·85; Br, 28·5. $C_{10}H_{12}O_3NBr$ requires N, 5·1; Br, 29·2%).

Di(*nitrophenoxy*)*alkanes* (*Table* 1).—The symmetrical *products* were prepared from potassium *p*-nitrophenoxide and the appropriate dibromide (cf. ref. 4). The unsymmetrical *compounds* were prepared from 5-*p*-nitrophenoxypentyl bromide and the appropriate phenol.

Di(*aminophenoxy*)*alkanes.*—Table 2 lists those *bases* and their *derivatives* which have not already been described elsewhere. All the amines were obtained by catalytic reduction of the nitro-compounds.

[25] Leonard, Felley, and Nicolaides, *J. Amer. Chem. Soc.*, 1952, **74**, 1700.

1 : 4-*Di*-(p-*acetamidophenoxy*)*but*-2-*yne*, prepared from *p*-acetamidophenol and 1 : 4-dibromobut-2-yne,[10] had m. p. 215—217° (lit.,[10] 218—220°). Acid hydrolysis gave **1 : 4-*di*-(p-*aminophenoxy*)*but*-2-*yne*** (84%), m. p. 103° (Found: C, 71·5; H, 6·1; N, 10·35. $C_{16}H_{16}O_2N_2$ requires C, 71·6; H, 6·0; N, 10·45%). It formed a ***dimethanesulphonate*** (Found: N, 5·95; S, 14·0. $C_{16}H_{16}O_2N_2,2CH_4O_3S$ requires N, 6·1; S, 13·9%).

1 : 6-*Di*-(p-*nitrophenoxy*)*hexa*-2 : 4-*diyne*.—A mixture of 1 : 6-dibromohexa-2 : 4-diyne [prepared from hexa-2 : 4-diyne-1 : 6-diol (24·5 g.) with phosphorus tribromide (46 g.)] and potassium *p*-nitrophenoxide (50 g.) in dry acetone (400 ml.) was refluxed for 5 hr. The product was crystallised from acetic acid, giving the ***nitro-compound*** (30%), m. p. 210—211° (Found: C, 61·2; H, 3·8; N, 8·1. $C_{18}H_{12}O_6N_2$ requires C, 61·4; H, 3·4; N, 8·0%).

1 : 6-*Di*-(p-*aminophenoxy*)*hexa*-2 : 4-*diyne*.—The above dinitro-compound (32·5 g.) was reduced by stannous chloride dihydrate (146 g.) in concentrated hydrochloric acid (160 ml.) and acetic acid (300 ml.). The base was isolated as the dihydrochloride (20 g.). The ***diamine*** (51%), after recrystallisation from ethanol, had m. p. 51° (Found: C, 73·7; H, 5·9; N, 9·5. $C_{18}H_{16}O_2N_2$ requires C, 73·9; H, 5·5; N, 9·6%).

Further reduction of the diamine (0·5 g.) in ethanol (20 ml.) over platinum oxide (0·1 g.) gave 1 : 6-di-(*p*-aminophenoxy)hexane (0·2 g.), m. p. and mixed m. p. 138—139°.

TABLE 2. *Compounds* $NH_2{\cdot}C_6H_4{\cdot}O{\cdot}[CH_2]_n{\cdot}O{\cdot}C_6H_4{\cdot}NH_2$.

Position of NH_2 groups	*n*	Deriv.	Yield (%)	M. p.	Solvent for recryst.	Formula	Found (%) N	Found (%) Cl	Required (%) N	Required (%) Cl
2 : 2′	3	Base	85	42—48°	Et_2O	$C_{15}H_{16}O_2N_2$	11·0	—	10·85	—
		2HCl		306—308		$C_{15}H_{16}O_2N_2,2HCl$	8·2	21·4	8·45	21·4
2 : 2′	5	Base	84	62	Aq. EtOH	$C_{17}H_{20}O_2N_2$	9·8	—	9·8	—
		2HCl		266 [a]		$C_{17}H_{20}O_2N_2,2HCl$	7·75	19·6	7·8	19·8
2 : 2′	8	Base	88	97	EtOH	$C_{20}H_{26}O_2N_2$	8·7	—	8·5	—
		2HCl		248	EtOH–Et_2O	$C_{20}H_{26}O_2N_2,2HCl$	7·0	17·6	7·0	17·7
3 : 3′	3	Base	78	148—150	EtOH	$C_{15}H_{16}O_2N_2$	10·6	—	10·85	—
		2HCl		252—254		$C_{15}H_{16}O_2N_2,2HCl,H_2O$	8·3	20·2	8·0	20·35
3 : 3′	5	Base	70	120	C_6H_6 or Aq. EtOH	$C_{17}H_{20}O_2N_2$	9·75	—	9·8	—
		2HCl		272—275		$C_{17}H_{20}O_2N_2,2HCl$	7·85	19·5	7·8	19·9
		Ac_2	60	176—178 [b]	AcOH	$C_{21}H_{26}O_4N_2,0{\cdot}25AcOH$	7·3		7·3	
4 : 2′	5	2HCl	96	238—242	EtOH–Et_2O	$C_{17}H_{22}O_2N_2,2HCl,0{\cdot}5H_2O$	7·8	19·0	7·6	19·3
4 : 3′	5	2HCl	78	225—230	EtOH–Et_2O	$C_{17}H_{22}O_2N_2,2HCl,0{\cdot}5H_2O$	7·8	19·0	7·6	19·3
4 : 4′	1	2HCl	—	240	—	$C_{12}H_{14}O_2N_2,2HCl$	9·2	23·5	9·25	23·4
4 : 4′	2	2HCl	—	270—280	—	$C_{14}H_{16}O_2N_2,2HCl$	8·8	21·9	8·8	22·4
4 : 4′	4	Ac_2	—	227—228	—	$C_{20}H_{24}O_4N_2$	7·9	—	7·85	—
4 : 4′	5	$(EtCO)_2$	100	167—169	EtOH	$C_{23}H_{30}O_4N_2$	7·05	—	7·0	—
		$(Me{\cdot}SO_2)_2$	79	183—185	$COMe_2$	$C_{19}H_{26}O_6N_2S_2$	6·4		6·3	
		Dithio-ureido	66	181—182 [c]	AcOH	$C_{19}H_{24}O_2N_4S_2$	13·45		13·8	
4 : 4′	7	2Me·SO_3H	—	247—249	EtOH–Et_2O	$C_{19}H_{26}O_2N_2,2CH_4O_3S$	5·4	—	5·5	—
4 : 4′	8	Base	79	130—132 [d]	EtOH or $CHCl_3$	$C_{20}H_{28}O_2N_2$	8·5	—	8·5	—
		2Me·SO_3H		276—278		$C_{20}H_{28}O_2N_2,2CH_4O_3S$	5·4		5·4	
4 : 4′	9	Base	82	82—83 [a]	Et_2O–Pet. [f]	$C_{21}H_{30}O_2N_2$	8·35	—	8·2	—
4 : 4′	10	Base	87	119 [d]	EtOH	$C_{22}H_{32}O_2N_2$	8·0	—	7·9	—
4 : 4′	12	Base	81	111—113	EtOH	$C_{24}H_{36}O_2N_2$	7·1	—	7·3	—
		2Me·SO_3H		220—250 [e]		$C_{24}H_{36}O_2N_2,2CH_4O_3S$	4·75		4·9	

[a] First prepared by Mr. S. S. Berg. [b] Found: C, 67·1; H, 7·0; Ac, 24·4. Required: C, 67·0; H, 7·3; Ac, 25·1%. [c] Prepared from the dihydrochloride and ammonium thiocyanate (Found: S, 15·6. Required: S, 15·8%). [d] First prepared by Mr. A. D. H. Self. [e] Found: S, 11·4. Required: S, 11·1%. [f] Pet. = light petroleum.

1 : 6-*Di*-(p-*acetamidophenoxy*)*hexa*-2 : 4-*diyne*.—This ***diyne*** (7 g.), obtained by refluxing 1 : 6-dibromohexa-2 : 4-diyne [prepared from hexa-2 : 4-diyne-1 : 6-diol (22 g.)], *p*-acetamidophenol (67 g.), and potassium carbonate (60 g.) in dry acetone (300 ml.) for 16 hr., crystallised from acetic acid and had m. p. 234° (decomp.) (Found: C, 69·4; H, 5·4; N, 7·1; Ac, 24·05.

XUM

$C_{22}H_{20}O_4N_2$,0·25AcOH requires C, 69·1; H, 5·4; N, 7·15; Ac, 24·7%). Hydrolysis with 10% aqueous hydrochloric acid gave the diamine, identical with the compound described above.

1 : 4-*Di*-(p-*nitrophenoxy*)*benzene*.—Quinol (27·5 g.) was added to a solution of potassium (19·5 g.) in absolute ethanol (250 ml.), *p*-chloronitrobenzene (158 g.) was then added and the mixture was heated in a metal bath to 200°, ethanol being distilled off. The residue was kept at 200° for 2·5 hr., steam-distilled to remove unchanged *p*-chloronitrobenzene, cooled, and filtered. The solid was washed with ethanol, then boiled with dioxan (500 ml.). The cooled suspension was filtered and the solid crystallised from acetic acid, to give **1 : 4-di-(*p*-nitrophenoxy)benzene** (20·7 g., 24%), m. p. 232—234° (Found: C, 61·5; H, 4·0; N, 8·1. Calc. for $C_{18}H_{12}O_6N_2$: C, 61·4; H, 3·4; N, 8·0%). Bayer [26] does not give an m. p. for this compound.

3-p-*Nitrophenoxy*cyclo*hexene*.—A mixture of 3-bromo*cyclo*hexene (21 g.) and potassium *p*-nitrophenoxide (26·2 g.) in dry carbon tetrachloride (400 ml.) and dry acetone (400 ml.) was refluxed for 6—8 hr., then filtered, and the filtrate was evaporated *in vacuo*. The residue, in ether, was washed successively with water, dilute aqueous sodium hydroxide, and water, and the ethereal solution was dried and evaporated. Crystallisation of the residue from light petroleum gave **3-p-*nitrophenoxy*cyclo*hexene*** (20 g.; 73·5%), m. p. 35—36° (Found: C, 66·0; H, 5·75; N, 6·6. $C_{12}H_{13}O_3N$ requires C, 65·75; H, 5·95; N, 6·4%).

3 : 6-*Di*-(p-*nitrophenoxy*)cyclo*hexene*.—(*a*) A mixture of 3-*p*-nitrophenoxy*cyclo*hexene (22 g.) and *N*-bromosuccinimide (19 g.) in dry carbon tetrachloride (200 ml.) was refluxed for 15—25 min., cooled, and filtered. Dry acetone (200 ml.) and finely ground potassium *p*-nitrophenoxide (20 g.) were added and the whole was stirred and refluxed for 48 hr. The re-filtered solution was evaporated to low bulk, ethanol was added to the residue, and the solid was filtered off, ground with sodium hydroxide solution, washed with water, and crystallised from acetic acid. Recrystallisation of the product (6 g.) from acetic acid gave 3 : 6-di-(*p*-nitrophenoxy)-*cyclo*hexene (5·3 g., 15%), m. p. 160—161°, raised by recrystallisation to 163—164°. (*b*) **3 : 6-**Dibromo*cyclo*hexene (7·1 g.) and dry finely powdered potassium *p*-nitrophenoxide (15 g.) in dry acetone (130 ml.) were refluxed for 12 hr., filtered hot, and diluted with water. The solid was filtered off, washed, and crystallised from acetic acid, giving the *nitro-compound* (8·1 g., 77%), m. p. 167—168° (Found: C, 60·4; H, 4·8; N, 7·9. $C_{18}H_{16}O_6N_2$ requires C, 60·6; H, 4·5; N, 7·9%), not depressed by a specimen prepared as in (*a*).

3 : 6-*Di*-(p-*aminophenoxy*)cyclo*hexene*.—**3 : 6-Di-(*p*-**nitrophenoxy)*cyclo*hexene (3 g.) in 85% acetic acid (40 ml.) was treated with reduced iron (3 g.). The suspension was boiled for 3 min., filtered while still hot, cooled, and slowly treated with concentrated hydrochloric acid (12 ml.) until the brown colour was discharged, then cooled again. After 2 hr., the hydrochloride was filtered off, and the filtrate was evaporated *in vacuo*. The residue, on treatment with a little water, gave more of the hydrochloride. The combined crops were dissolved in the minimum of water, treated with concentrated hydrochloric acid, cooled, and filtered. The hydrochloride (1·5 g., 48%) was washed with acetone and dried. Treatment with aqueous sodium hydroxide and crystallisation from ethanol then gave the *base* (42%), m. p. 123—124° (Found: C, 72·7; H, 6·6; N, 9·3. $C_{18}H_{20}O_2N_2$ requires C, 73·0; H, 6·8; N, 9·5%). It formed a *dihydrochloride* (Found: N, 7·6; Cl, 18·9. $C_{18}H_{20}O_2N_2$,2HCl requires N, 7·6; Cl, 19·25%) and a *dimethanesulphonate* (Found: N, 5·9; S, 13·2. $C_{18}H_{20}O_2N_2$,2CH_4O_3S requires N, 5·75; S, 13·1%).

1 : 4-*Di*-(p-*aminophenoxy*)cyclo*hexane*.—(*a*) **3 : 6-**Di-(*p*-aminophenoxy)*cyclo*hexene (0·82 g.) in ethanol (30 ml.) was reduced over platinum oxide (0·1 g.). **1 : 4-*Di*-(p-*aminophenoxy*)cyclo*hexane*** after recrystallisation from ethanol had m. p. 157—159° (Found: C, 72·4; H, 7·5; N, 9·4. $C_{18}H_{22}O_2N_2$ requires C, 72·5; H, 7·4; N, 9·4%). It formed a *dimethanesulphonate* (Found: N, 5·9; S, 13·0. $C_{18}H_{22}O_2N_2$,2CH_4O_3S requires N, 5·7; S, 13·1%). (*b*) **3 : 6-Di-(*p*-**nitrophenoxy)*cyclo*hexene (7·1 g.) in methanol (300 ml.) was reduced over 1% palladium–calcium carbonate (5 g.), giving the diamine (51%), m. p. 157—159°, not depressed by a sample prepared as in (*a*). (*c*) The same diamine, m. p. 159—161°, was obtained by reduction of **1 : 4-**di-(*p*-nitrophenoxy)*cyclo*hexane over Raney nickel in dimethylformamide. **1 : 4-Di-(*p*-**aminophenoxy)*cyclo*hexane (1 g.) yielded *trans*-**1 : 4-**dibromo*cyclo*hexane, m. p. 112° (0·2 g.), identical with an authentic specimen,[27] when refluxed for 1 hr. with 52% aqueous hydrobromic acid.

Condensation of 5-p-*Nitrophenoxypentyl Bromide with Quinol*.—A solution of potassium hydroxide (11·2 g.) in ethanol was slowly added to a stirred, refluxing solution of 5-*p*-nitrophenoxypentyl bromide (57·6 g.) and quinol (22 g.) in ethanol. The mixture was refluxed

[26] Bayer, D.R.-P. 178,803.
[27] Zelmsky and Kozeschkow, *Ber.*, 1927, **60**, 1103.

overnight, then concentrated, and the residue was treated with water. The solid product was extracted with boiling N-sodium hydroxide (2 × 500 ml.). Acidification of the alkaline extract gave 1-p-*hydroxyphenoxy*-5-p-*nitrophenoxypentane* (21 g., 32%) which, after recrystallisation from chloroform, had m. p. 141—143° (Found: N, 4·5. $C_{17}H_{19}O_5N$ requires N, 4·4%).

The alkali-insoluble material was recrystallised from acetic acid (charcoal), yielding p-*di*-(5-p-*nitrophenoxypentyloxy*)*benzene* (22 g., 41%), m. p. 138—139° (after recrystallisation from chloroform) (Found: N, 5·1. $C_{28}H_{32}O_8N_2$ requires N, 5·35%). For maximum conversion into the bis-condensation product, a higher proportion of bromide would have been advantageous but, in this instance, both products were required for further work.

3-*Methylglutaraldehyde*.—2-Ethoxy-3 : 4-dihydro-4-methylpyran (142 g.) (kindly supplied by Dr. B. J. Heywood) was stirred with 4N-sulphuric acid (250 ml.) for 4 hr. at room temperature. The mixture was poured into saturated potassium carbonate solution, then extracted with ether, and the washed and dried extract was distilled, yielding the dialdehyde (83 g.), b. p. 87—92°/18 mm. (lit.,[28] b. p. 140—160°/20 mm.).

3-*Methylpentane*-1 : 5-*diol*.—3-Methylglutaraldehyde (57 g.) in ethanol (200 ml.) was reduced over Raney nickel at 100°/730 lb. The product was distilled, giving the diol (39·55 g., 67%), b. p. 140°/16 mm. (lit.,[9] b. p. 134—137°/6 mm.). Refluxing with 50% hydrobromic acid and concentrated sulphuric acid gave 1 : 5-dibromo-3-methylpentane (60·4 g., 74%), b. p. 106°/16 mm. (Found: Br, 65·6. Calc. for $C_6H_{12}Br_2$: Br, 65·6%) (lit.,[7] 97—98·5°/10 mm.).

1 : 1-*Di*-(2-*hydroxyethyl*)cyclo*hexane*.—*cyclo*Hexylidenediacetic acid [29a] (39·5 g.) in dry tetrahydrofuran (300 ml.) was reduced by lithium aluminium hydride (27·35 g.) in dry ether (1 l.). The product was distilled, giving the *diol* (29·6 g., 87%), b. p. 176—186°/14 mm. (Found: C, 68·9; H, 11·2. $C_{10}H_{20}O_2$ requires C, 69·7; H, 11·7%). The *ditoluene*-p-*sulphonate* had m. p. 69—70° (Found: S, 13·05. $C_{24}H_{32}O_6S_2$ requires S, 13·35%).

1 : 1-*Di*-(2-*bromoethyl*)cyclo*hexane*.—A mixture of the preceding diol (19·6 g.) and 50% hydrobromic acid (75 ml.) was treated slowly with concentrated sulphuric acid (37 ml.), and heated on the steam-bath for 20 hr. Distillation of the product, isolated in the usual way, gave the *dibromide* (64%), b. p. 166—173°/13 mm. A redistilled specimen had b. p. 179—182°/20 mm. (Found: C, 40·7; H, 6·0; Br, 52·1. $C_{10}H_{18}Br_2$ requires C, 40·3; H, 6·1; Br, 53·6%). In a similar experiment under reflux (6 hr.), the yield of dibromide fell to 31%, and a low-boiling by-product (51%) was formed. After fractionation from solid potassium hydroxide the latter had b. p. 87°/12 mm. (Found: C, 77·2; H, 11·8. $C_{10}H_{18}O$ requires C, 77·8; H, 11·8%) and was presumably cyclo*hexane*spiro-4-*tetrahydropyran* (II).

TABLE 3. *Compounds* p-NH_2·C_6H_4·X·C_6H_4·NH_2-*p*.

−X−	Deriv.	Yield (%)	M. p.	Solvent for recryst.	Formula	Found (%) N	Reqd. (%) N
p-O·CH_2·C_6H_4·CH_2O	Base	70	143—144°	EtOH	$C_{28}H_{26}O_2N_2$	8·75	8·75
p-O·[CH_2]$_5$·O·C_6H_4·O·[CH_2]$_5$·O	Base	61	133	EtOAc–Pet [a]	$C_{28}H_{34}O_4N_2$	5·8 [c]	6·0
O·[CH_2]$_3$·O·[CH_2]$_2$·O	Base	—	80	—	$C_{16}H_{26}O_2N_2$	9·7	9·7
	2Me·SO_3H	—	237—239 [b]		$C_{16}H_{26}O_2N_2$,2CH_4O_3S	5·9	5·8
O·CH_2·CH(OH)·CH_2·O	Base	63	114	EtOH	$C_{13}H_{18}O_3N_2$	10·05	10·2
	2Me·SO_3H		230		$C_{13}H_{18}O_3N_2$,2CH_4O_3S	5·9	6·0
O·[CH_2]$_3$·CHPh·[CH_2]$_2$·O	2Me·SO_3H	86	194—200	EtOH–Et_2O	$C_{23}H_{34}O_2N_2$,2CH_4O_3S	5·0	5·05
O·[CH_2]$_3$·CMe_2·[CH_2]$_2$·O	Base	97	55—56	$CHCl_3$–Pet	$C_{15}H_{30}O_2N_2$	8·8	8·9
	2Me·SO_3H		188—192	EtOH–Et_2O	$C_{15}H_{30}O_2N_2$,2CH_4O_3S	5·5 [d]	5·5
[CH_2]$_5$>C([CH_2·CH_2·O)$_2$	2Me·SO_3H	87 [b]	214—216	EtOH	$C_{23}H_{36}O_2N_2$,2CH_4O_3S	5·2	5·1

[a] With decomp. [b] Pet = light petroleum. [c] Over Raney nickel in dimethylformamide (Found: S, 12·1. Required: S, 11·75%). [c] Found: C, 72·2; H, 8·3. Required: C, 72·5; H, 7·8%. [d] Found: C, 49·4; H, 6·9. Required: C, 49·8; H, 6·7%.

[28] Riban, *Bull. Soc. chim. France*, 1872, **18**, 63.
[29] Majer, U.S.P. 1,978,433/1934.
[29a] Vogel, *J.*, 1934, 1761.

The following nitro-compounds were prepared by condensation of potassium *p*-nitrophenoxide with, except where stated, the appropriate dibromide in ethylene glycol or 2-ethoxyethanol: trans-1 : 4-*di*-(p-*nitrophenoxy*)cyclo*hexane* (from the *trans*-ditoluene-*p*-sulphonate [18]) (7·5%), m. p. 208—210° (from acetic acid) (Found: C, 60·2; H, 5·0; N, 7·8. $C_{18}H_{18}O_6N_2$ requires C, 60·3; H, 5·0; N, 7·8%); p-*di*-(p-*nitrophenoxymethyl*)*benzene* (52%), m. p. 222—225° (from acetic acid) (Found: N, 7·3. $C_{20}H_{16}O_6N_2$ requires N, 7·4%); 1 : 5-*di*-(p-*nitrophenoxy*)-3-*phenylpentane* (25%), m. p. 132° (from ethanol) (Found: N, 6·8. $C_{23}H_{22}O_6N_2$ requires N, 6·7%); 3 : 3-*dimethyl*-1 : 5-*di*-(p-*nitrophenoxy*)*pentane* (51%), m. p. 81° (from ethanol) (Found: N, 7·8. $C_{19}H_{22}O_6N_2$ requires N, 7·5%); and 1 : 1-*di*-(2-p-*nitrophenoxyethyl*)cyclo*hexane* (46% overall from glycol), m. p. 115—117° (from acetic acid) (Found: N, 6·9. $C_{22}H_{26}O_6N_2$ requires N, 6·8%). The corresponding *amines* (Table 3) were prepared by catalytic reduction of the nitro-compounds.

1 : 3-*Di*-(4-*acetamido*-3-*nitrophenoxy*)*propane* (*Experiment by* Mr. S. S. Berg).—4-Hydroxy-2-nitroacetanilide [24] (372 g.), 1 : 3-dibromopropane (202 g.), anhydrous potassium carbonate (151·8 g.), potassium iodide (1 g.), and anhydrous acetone (10 l.) were stirred and refluxed for 24 hr., cooled, and filtered. The solid was washed with N-sodium hydroxide, water, and ethanol, and recrystallised from acetic acid (charcoal), giving yellow needles (300 g., 70%), m. p. 203—204° (Found: C, 52·4; H, 4·75; N, 12·8. $C_{19}H_{20}O_8N_4$ requires C, 52·8; H, 4·6; N, 12·95%). Evaporation of the acetone mother-liquors and extraction of the residue with light petroleum (b. p. 60—80°) gave 3-(4-*acetamido*-3-*nitrophenoxy*)*propyl bromide* (6·1 g.). After repeated recrystallisation from light petroleum (b. p. 60—80°), it formed yellow needles, m. p. 81—82° (Found: N, 8·8; Br, 25·0. $C_{11}H_{13}O_4N_2Br$ requires N, 8·8; Br, 25·2%). 1 : 5-*Di*-(4-*acetamido*-3-*nitrophenoxy*)*pentane*, similarly prepared, had m. p. 194—195° (Found: C, 54·6; H, 5·05; N, 12·4. $C_{21}H_{24}O_8N_4$ requires C, 54·8; H, 5·2; N, 12·2%).

1 : 3-*Di*-(4-*amino*-3-*nitrophenoxy*)*propane* (*Experiment by* Mr. S. S. Berg).—Hydrogen chloride was bubbled for 1·25 hr. through a suspension of the foregoing compound in boiling ethanol. The hydrochloride, which separated, was treated with alkali, and the *base* was crystallised from 2-ethoxyethanol, yielding red prisms (91%), m. p. 188—189° (Found: C, 51·6; H, 4·55; N, 16·5. $C_{15}H_{16}O_6N_4$ requires C, 51·7; H, 4·6; N, 16·1%). 1 : 5-*Di*-(4-*amino*-3-*nitrophenoxy*)*pentane*, similarly prepared, had m. p. 134—135° (Found: C, 54·1; H, 5·45; N, 14·7. $C_{17}H_{20}O_6N_4$ requires C, 54·25; H, 5·3; N, 14·9%).

1 : 5-*Di*-(4-*acetamido*-3-*aminophenoxy*)*pentane*.—The nitro-compound was reduced catalytically to the *amine*, m. p. 180—181° (Found: N, 14·1. $C_{21}H_{28}O_4N_4$ requires N, 14·0%).

1 : 5-*Di*-(3-*acetamido*-4-*nitrophenoxy*)*pentane*.—Nitric acid (*d* 1·5; 6·3 ml.) was added during 45 min. to a stirred suspension of 1 : 5-di-(*m*-acetamidophenoxy)pentane (13 g.) in acetic anhydride (100 ml.) at 5—10°. After a further 15 min., the mixture was filtered through a sintered-glass funnel to remove unchanged material, and the filtrate was poured into ice-water and kept for 2 hr. The aqueous layer was decanted and the residual gum was dissolved in acetone. The solid which separated was filtered off, washed with acetone and ether, and

Table 4. *Compounds* O_2N—(R, R′)—$O\cdot[CH_2]_n\cdot O$—(R″, R)—NO_2

				Yield		Solvent for		Found (%)		Reqd. (%)	
n	R	R′	R″	(%)	M. p.	recryst.	Formula	N	Hal	N	Hal
3	H	Br	H	50 *	154°	EtOH	$C_{15}H_{13}O_6N_2Br$	7·2	20·0	7·1	20·15
5	H	Cl	Cl	34	118—120	AcOH	$C_{17}H_{14}O_6N_2Cl_2$	6·7	17·1	6·75	17·1
5	Cl	H	H	47	92—93	AcOH	$C_{17}H_{14}O_6N_2Cl_2$	7·1	16·85	6·75	17·1
5	Me	H	H	39	100—102	EtOH	$C_{19}H_{22}O_6N_2$	7·75	—	7·5	—
5	H	OMe	OMe	85	126—128	AcOH	$C_{19}H_{22}O_8N_2$	6·8	—	6·9	—

* From 3-*p*-nitrophenoxypropyl bromide and 2-bromo-4-nitrophenol in ethanol.

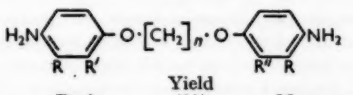
crystallised from acetic acid, giving 1 : 5-*di*-(3-*acetamido*-4-*nitrophenoxy*)*pentane* (1·5 g., 9%), m. p. 154—155° (Found: C, 54·6; H, 5·0; N, 12·5. $C_{21}H_{24}O_8N_4$ requires C, 54·8; H, 5·2; N, 12·2%). Its orientation was established by reduction and acetylation to 1 : 5-*di*-(3 : 4-*diacetamidophenoxy*)*pentane*, m. p. 186—188° (Found: N, 11·4; Ac, 32·9. $C_{25}H_{32}O_6N_4$ requires N, 11·6; Ac, 35·5%), identical with specimens prepared from authentic 1 : 5-di-(3 : 4-diaminophenoxy)pentane and from 1 : 5-di-(4-acetamido-3-aminophenoxy)pentane. Other *nitro-compounds* are listed in Table 4, and the corresponding *amines* in Table 5.

ON-*Diacetyl*-p-iso*propylaminophenol*.—*p-iso*Propylaminophenol [29] (30·2 g.) was boiled with acetic anhydride (100 ml.) for 1 hr., excess of reagent then being removed under reduced pressure. The residue, after trituration with light petroleum, gave an almost quantitative yield of crude product, pure enough for hydrolysis (see below). Crystallisation from light petroleum gave ON-*diacetyl*-p-iso*propylaminophenol* in prisms, m. p. 78—80° (Found: N, 6·0. $C_{13}H_{17}O_3N$ requires N, 5·95%).

N-*Acetyl*-p-iso*propylaminophenol*.—The above *ON*-diacetyl compound (1·9 g.) was shaken with 2N-sodium hydroxide (10 ml.), and the solution obtained was filtered and acidified with acetic acid. The washed and dried product (1·2 g., 77%, m. p. 150°) crystallised from acetone–light petroleum, giving *N-acetyl*-p-iso*propylaminophenol* in needles, m. p. 154° (Found: N, 7·0. $C_{11}H_{15}O_2N$ requires N, 7·25%).

1 : 5-*Di*-(p-iso*propylaminophenoxy*)*pentane*.—A solution of 1 : 5-di-(*p*-aminophenoxy)pentane (2 g.) in acetone (50 ml.) was boiled under reflux for 20 hr., then reduced catalytically over platinum oxide. When the initial rapid uptake of hydrogen had ceased and there was only a slow uptake due to reduction of the solvent, the mixture was filtered and evaporated. Chromatography of the residue in light petroleum (b. p. 60—80°) over alumina gave 1 : 5-*di*-(p-iso*propylaminophenoxy*)*pentane* (41%), m. p. 49—50° (after recrystallisation from ether–light petroleum) (Found: C, 74·8; H, 9·2; N, 7·5. $C_{23}H_{34}O_2N_2$ requires C, 74·6; H, 9·3; N, 7·6%). The *diacetyl derivative* had m. p. 98—100° [from light petroleum (b. p. 60—80°)] (Found: N, 6·1. $C_{27}H_{38}O_3N_2$ requires N, 6·2%).

1-p-*Di*(iso*propylamino*)*phenoxy*-5-p-iso*propylaminophenoxypentane*.—A mixture of the foregoing bis*iso*propyl compound (2·3 g.), anhydrous sodium carbonate (1 g.), *iso*propyl bromide (10 ml.), and ethanol (15 ml.) was refluxed for 20 hr., then evaporated. The residue was basified

TABLE 5. *Compounds* 

No.	*n*	R	R′	R″	Deriv.	Yield (%)	M. p.	Solvent for recryst.
1	3	H	Br	H	Base	—	103—105°	$CHCl_3$–Pet [d]
2	—	—	—	—	2HCl	73	282—284° [a]	Dil. HCl
3	3	H	NH_2	NH_2	Base	78	118—120	EtOH
4	3	NO_2	H	H	Base	—	185	$COMe_2$
5	5	H	Cl	Cl	Base	85	95—96	EtOH
6	—	—	—	—	2HCl	—	270—280° [a]	—
7	5	Cl	H	H	2Me·SO_3H	70	202—206	EtOH–Et_2O
8	5	Me	H	H	Base	79	69—71	C_6H_6–Pet [d]
9	—	—	—	—	2HCl	—	246—248	—
10	5	NH_2	H	H	Base	95	105—106° [a,b]	Pr^iOH
11	5	NHAc	H	H	Base	64	179	MeOH
12	5	H	OMe	OMe	Base	88	106—107	EtOH
13	—	—	—	—	2Me·SO_3H	—	228—230° [c]	—

		Found (%)				Required (%)			
No.	Formula	C	H	N	Hal	C	H	N	Hal
1	$C_{15}H_{17}O_2N_2Br$	—	—	—	23·5	—	—	—	23·7
2	$C_{15}H_{17}O_2N_2Br,2HCl$	—	—	6·6	17·9	—	—	6·8	17·3
3	$C_{15}H_{20}O_2N_4$	—	—	19·6	—	—	—	19·4	—
4	$C_{15}H_{16}O_6N_4$	52·05	4·8	16·3	—	51·8	4·6	16·1	—
5	$C_{17}H_{20}O_2N_2Cl_2$	—	—	8·0	—	—	—	7·9	—
6	$C_{17}H_{20}O_2N_2Cl_2,2HCl$	—	—	6·5	32·7	—	—	6·5	33·1
7	$C_{17}H_{20}O_2N_2Cl_2,2CH_4O_3S,2H_2O$	—	—	5·2	12·0	—	—	4·8	12·15
8	$C_{19}H_{24}O_2N_2$	—	—	8·8	—	—	—	8·9	—
9	$C_{19}H_{24}O_2N_2,2HCl$	58·5	6·85	7·2	18·3	58·9	7·2	7·2	18·35
10	$C_{17}H_{24}O_2N_4$	—	—	17·6	—	—	—	17·7	—
11	$C_{21}H_{32}O_4N_4$	62·7	7·2	14·35	—	63·0	7·0	14·0	—
12	$C_{19}H_{26}O_4N_2$	—	—	8·0	—	—	—	8·1	—
13	$C_{19}H_{26}O_4N_2,2CH_4O_3S$	—	—	5·2	—	—	—	5·2	—

[a] With decomp. [b] First prepared by Mr. S. S. Berg. [c] From 1 : 5-di-(4-amino-3-nitrophenoxy)-pentane over PtO_2 in dioxan. [d] Found: S, 11·9. Required: S, 11·9%. [e] Pet = light petroleum.

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and extracted with ether. The washed and dried extract was evaporated and the residue was chromatographed in light petroleum, yielding the *triisopropyl derivative* (0·7 g.), m. p. 56—57° (Found: C, 75·8; H, 9·8; N, 6·9. $C_{34}H_{46}O_2N_2$ requires C, 75·7; H, 9·8; N, 6·8%).

1 : 5-*Di*-(p-2-*methoxyethylaminophenoxy*)*pentane*.—A mixture of 1 : 5-di-(*p*-aminophenoxy)-pentane (31·4 g.), 2-methoxyethyl chloride [30] (41·5 g., 4 mol.), and calcium carbonate (30 g.) in water (250 ml.) was refluxed for 24 hr., cooled, shaken with chloroform, and filtered. The chloroform solution was separated, dried, concentrated, and treated with ether. The product, which separated, was recrystallised from ether and aqueous methanol and chromatographed in chloroform–benzene over alumina. The purified *base* (23%) had m. p. 68—69° (Found: C, 68·6; H, 8·4; N, 6·9. $C_{23}H_{34}O_4N_2$ requires C, 68·6; H, 8·5; N, 7·0%). It failed to give a diazo-test for aromatic amino-groups.

1 : 5-*Di*-[p-(*diethylaminoethyl*)*aminophenoxy*]*pentane*.—An intimate mixture of 1 : 5-di-(*p*-aminophenoxy)pentane (56·4 g.) and 2-diethylaminoethyl chloride hydrochloride (80 g.) was heated at 135° for 20 hr. A solution of the product in warm water was basified with 50% sodium hydroxide solution and extracted with ether (3 × 600 ml.), and the combined extracts were washed with water, dried, and evaporated. The residue was distilled in small batches and the fractions of b. p. 260—280°/0·05 mm. (20 g.) were combined and redistilled, to give the *amine* (13·6 g.), b. p. 270—280°/0·05 mm. (Found: C, 71·9; H, 9·9; N, 11·5. $C_{29}H_{48}O_2N_4$ requires C, 72·0; H, 9·9; N, 11·6%).

1 : 5-*Di*-(p-*succinimidophenoxy*)*pentane*.—A mixture of 1 : 5-di-(*p*-aminophenoxy)pentane (5 g.) and succinic anhydride (25 g.) was boiled under reflux for 15 min. The cooled product was extracted with boiling water and with boiling ethanol, and the insoluble residue was crystallised from acetic acid, giving 1 : 5-*di*-(p-*succinimidophenoxy*)*pentane* (7·2 g., 91·5%), m. p. 204·5—205·5° (Found: C, 66·5; H, 5·85; N, 6·0. $C_{25}H_{26}O_6N_2$ requires C, 66·7; H, 5·8; N, 6·2%).

1 : 5-*Di*-(p-*pyrrolidinophenoxy*)*pentane*.—(*a*) 1 : 5-Di-(*p*-aminophenoxy)pentane (28·6 g.) 1 : 4-dibromobutane (43·2 g., 2 mol.), and sodium carbonate (21·2 g., 4 equivs.) in ethanol (400 ml.) were refluxed overnight, then treated with a little dilute sodium hydroxide, cooled, and filtered. The product was extracted with chloroform, which was washed, concentrated, diluted with ethanol, cooled, and filtered. 1 : 5-*Di*-(p-*pyrrolidinophenoxy*)*pentane* (76%), after recrystallisation from benzene–light petroleum, had m. p. 126° (partially melts at 120—121°) (Found: C, 76·3; H, 8·6; N, 7·2. $C_{25}H_{34}O_2N_2$ requires C, 76·1; H, 8·7; N, 7·1%). The compound is probably dimorphic. (*b*) 1 : 5-Di-(*p*-succinimidophenoxy)pentane (7·1 g.) in tetrahydrofuran (200 ml.) was reduced with lithium aluminium hydride (8 g.) in tetrahydrofuran (200 ml.). The base (49%) had m. p. 126—127° (partially melts at 120—121°).

1 : 5-*Di*-(p-*piperidinophenoxy*)*pentane*, prepared (47%) from 1 : 5-di-(*p*-aminophenoxy)-pentane and 1 : 5-dibromopentane by method (*a*) above, and crystallised from ether, had m. p. 73—74° (Found: C, 76·4; H, 8·7; N, 6·6. $C_{27}H_{38}O_2N_2$ requires C, 76·7; H, 9·1; N, 6·6%).

1 : 5-*Di*-(p-*morpholinophenoxy*)*pentane*.—Di-(2-chloroethyl) ether (28·6 g.), 1 : 5-di-(*p*-aminophenoxy)pentane (28·6 g.), and sodium carbonate (29·2 g.) in 2-ethoxyethanol (100 ml.) were refluxed for 20 hr., then poured into water. The product was taken up in chloroform, which was washed, dried, and evaporated, and the residue was heated for 1 hr. on the steam-bath with acetic anhydride (50 ml.) and pyridine (50 ml.). The resulting solution was poured into dilute hydrochloric acid, which was extracted with chloroform, then filtered and basified. The product was filtered off, washed, and crystallised from ethanol, giving 1 : 5-*di*-(p-*morpholinophenoxy*)*pentane* (44%), m. p. 115—117° (Found: C, 70·4; H, 7·9; N, 6·6. $C_{25}H_{34}O_4N_2$ requires C, 70·4; H, 8·0; N, 6·6%). When a similar experiment was conducted in ethanol a mixture of unchanged base and the monomorpholino-compound was obtained. Acetylation removed the insoluble 1 : 5-di-(*p*-acetamidophenoxy)pentane (6·9 g., 19%) from the acid-soluble 1-p-*acetamidophenoxy*-5-*morpholinophenoxypentane* (8·45 g., 21%), which after recrystallisation from ethanol had m. p. 136—137° (Found: C, 69·5; H, 7·7; N, 6·9. $C_{23}H_{30}O_4N_2$ requires C, 69·3; H, 7·6; N, 7·0%). A similar experiment, carried out without any solvent but with heating for 8 hr. at 135—140°, gave the dimorpholino-compound (29%).

1 : 5-*Di*-(p-*pyrid*-2′-*ylaminophenoxy*)*pentane*.—1 : 5-Di-(*p*-aminophenoxy)pentane (4·5 g.), 2-bromopyridine (6·5 g.), anhydrous potassium carbonate (1·7 g.), and copper bronze (0·9 g.) were heated for 180° for 20 min., after which evolution of gas ceased. The cooled mixture was treated with aqueous sodium hydroxide and extracted with chloroform. The washed extract was evaporated and the residue was crystallised from ethyl acetate–light petroleum, giving

[30] Bennett and Heathcoat, *J.*, 1929, 270.

1 : 5-*di*-(p-*pyrid*-2′-*ylaminophenoxy*)*pentane* (72%), m. p. 150—152° (Found: N, 12·6. $C_{27}H_{28}O_2N_4$ requires N, 12·7%).

1 : 5-*Di*-(p-4′-*methylthiazol*-2′-*ylaminophenoxy*)*pentane*.—1 : 5-Di-(*p*-thioureidophenoxy)-pentane (8·1 g.) and twice redistilled chloroacetone (6·1 g.) were heated in ethanol (20 ml.) under reflux for 4 hr., then slowly treated with 2N-sodium hydroxide (approx. 100 ml.). The product was filtered off, washed with water, and dried. Recrystallisation from chloroform–light petroleum gave **1 : 5-*di*-(p-4′-*methylthiazol*-2′-*ylaminophenoxy*)*pentane*** (78%), m. p. 188—190° (Found: N, 11·8; S, 13·4. $C_{25}H_{28}O_2N_4S_2$ requires N, 11·7; S, 13·3%).

Sodium Formaldehyde Bisulphite Derivative of* 1 : 5-*Di*-(p-*aminophenoxy*)*pentane*.**—1 : 5-Di-(*p*-aminophenoxy)pentane (10 g.) and sodium formaldehyde bisulphite (13 g.) were heated in water (100 ml.) on the steam-bath for 1 hr., then treated with charcoal, filtered, and cooled. The ***sodium formaldehyde bisulphite derivative (61%) was filtered off, washed with a little water and acetone, and dried. It decomposed at 270—290° (Found: N, 5·3. $C_{19}H_{24}O_8N_2S_2Na_2$ requires N, 5·4%).

The following amines and derivatives are not fully described elsewhere: **1 : 3-*di*-(p-*methylaminophenoxy*)*propane***, m. p. 90—91° (from ethanol) (Found: C, 71·4; H, 7·7; N, 10·0. $C_{17}H_{22}O_2N_2$ requires C, 71·3; H, 7·7; N, 9·8%) {***diacetyl derivative***, m. p. 109—111° [from light petroleum (b. p. 100—120°)] (Found: C, 67·9; H, 7·35; N, 7·5. $C_{21}H_{26}O_4N_2$ requires C, 68·1; H, 7·1; N, 7·6%)}; **1 : 3-*di*-(p-*dimethylaminophenoxy*)*propane***, m. p. 67—69° (from ethanol) (Found: N, 8·9. $C_{19}H_{26}O_2N_2$ requires N, 8·9%); **1 : 8-*di*-(p-*methylaminophenoxy*)*octane***, m. p. 87—87·5° [from light petroleum (b. p. 80—100°)] (Found: C, 74·3; H, 9·1; N, 7·6. $C_{22}H_{32}O_2N_2$ requires C, 74·1; H, 9·1; N, 7·85%) {***diacetyl derivative***, m. p. 86—88° (from light petroleum) (Found: N, 6·2. $C_{26}H_{36}O_4N_2$ requires N, 6·4%)}; **1 : 8-*di*-(p-*dimethylaminophenoxy*)*octane***, m. p. 126—127° (from chloroform–ethanol) (Found: C, 75·3; H, 9·4; N, 7·3. $C_{24}H_{36}O_2N_2$ requires C, 75·0; H, 9·5; N, 7·3%) {***bismethiodide***, m. p. 195—197° (from water) (Found: N, 4·0; I, 36·4. $C_{26}H_{42}O_2N_2I_2,2H_2O$ requires N, 4·0; I, 36·1%)}; **1 : 5-*di*-(p-*ethylmethylaminophenoxy*)*pentane dipicrate***, m. p. 165—167°. (Found: N, 13·6. $C_{23}H_{34}O_2N_2,2C_6H_3O_7N_3$ requires N, 13·5%); **1 : 3-*di*-(p-*diethylaminophenoxy*)*propane***, b. p. 244—248°/0·1 mm. (Found: C, 74·5; H, 9·1; N, 7·75. $C_{23}H_{34}O_2N_2$ require C, 74·6; H, 9·3; N, 7·55%); and **1 : 5-*di*-(p-*di*-n-*propylaminophenoxy*)*pentane disulphate***, m. p. 125—127° (Found: N, 4·3; S, 10·3. $C_{29}H_{46}O_2N_2,2H_2SO_4$ requires N, 4·3; S, 9·9%).

Di*-(p-*nitrophenyl*) *Glutarate*.**—Glutaryl chloride (16·9 g.), dissolved in dry acetone, was slowly added to a suspension of dry potassium *p*-nitrophenoxide (36·3 g.) in dry acetone, the resulting mixture then being heated under reflux for 4 hr., concentrated, and poured into sodium hydrogen carbonate solution. The product was filtered off, washed, and dried ***in vacuo. Crystallisation from ethyl acetate gave ***di*-(p-*nitrophenyl*) *glutarate*** (38%), m. p. 138—140° (Found: N, 7·65. $C_{17}H_{14}O_8N_2$ requires N, 7·5%). A further 2·1 g. (6%), m. p. 130—132°, were obtained from the mother-liquors.

Di*-(2-p-*nitrophenoxyethyl*) *ether (86%) had m. p. 153° (Found: N, 8·1. $C_{16}H_{16}O_7N_2$ requires N, 8·05%).

1 : 5-*Di*-(p-*nitrophenyl*)*penta*-2 : 4-*dien*-1-*one*.—A solution of *p*-nitrocinnamaldehyde (7·08 g.) in hot ethanol (100 ml.) was slowly added to a stirred solution of *p*-nitroacetophenone (6·6 g.) in hot ethanol (100 ml.), containing a few drops of aqueous potassium hydroxide. The cooled suspension was filtered and the product was crystallised from ethyl methyl ketone and from acetone, giving **1 : 5-*di*-(p-*nitrophenyl*)*penta*-2 : 4-*dien*-1-*one*** (48%), m. p. 210—212° (Found: N, 8·8. $C_{17}H_{12}O_5N_2$ requires N, 8·6%).

1 : 5-*Di*-(p-*acetamidophenyl*)-3-*acetoxypentane*.—When 1 : 5-di-(*p*-nitrophenyl)penta-1 : 4-dien-3-one [31] (2·5 g.) was reduced over Raney nickel in ethyl acetate at 100°/420 lb. per sq. in., the product did not crystallise. It was heated with acetic anhydride in pyridine at 100°, yielding **1 : 5-*di*-(p-*acetamidophenyl*)-3-*acetoxypentane*** (1·75 g.), m. p. 126—128°. Recrystallisation from ethanol–ether gave needles, m. p. 128—130° (Found: C, 69·6; H, 7·1; N, 7·1; Ac, 31·8. $C_{23}H_{28}O_4N_2$ requires C, 69·7; H, 7·1; N, 7·1; Ac, 32·5%).

1-(2 : 4-*Dinitrophenyl*)-5-p-*nitrophenoxypentane*.—5-Phenylpentyl bromide (1·85 g.) was slowly added to nitric acid (*d* 1·5; 10 ml.) kept at between 0° and −10° by addition of solid carbon dioxide. The solution was set aside for 1 hr. at room temperature, then diluted with water. The oil separating was extracted into ether, which was washed with warm water and sodium hydrogen carbonate solution, dried and evaporated.

[31] Petrenko-Kritschenko, *Ber.*, 1898, **31**, 1508.

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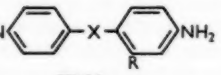
The oily bromide thus obtained and potassium *p*-nitrophenoxide (2 g.) in ethanol (10 ml.) were refluxed for 20 hr., then poured into 2N-sodium hydroxide and extracted with chloroform. The washed and dried extract was evaporated and the residue chromatographed in benzene. Recrystallisation of the product from acetone–ethanol gave the *trinitro-compound* (1·2 g., 39% overall), m. p. 78° (Found: N, 11·3. $C_{17}H_{17}O_7N_3$ requires N, 11·2%).

5-p-*Nitrophenylpentyl Bromide*.—5-Phenylpentyl bromide (22·7 g.) was added during 40 min. to stirred nitric acid (*d* 1·5; 45 ml.) at −50° to −55°. The mixture was immediately poured into 50% sodium hydroxide solution (60 ml.) and ice, and the product was extracted with ether. The washed and dried extract was evaporated and the residue was distilled in three portions. The combined distillates (17·3 g.) of b. p. 141—180°/0·07 mm. were redistilled, giving as principal fractions: (i) 5·8 g., b. p. 155—165°/0·1 mm. (Found: N, 5·3; Br, 28·2. $C_{11}H_{14}O_2NBr$ requires N, 5·15; Br, 29·4%), and (ii) 7·75 g., b. p. 165—190°/0·1 mm. (Found: N, 5·9; Br, 27·65%). The structure of the crude 5-*p*-nitrophenylpentyl bromide was proved by successive condensation with fused potassium acetate in acetic acid, hydrolysis with ethanolic sodium hydroxide, and oxidation with alkaline potassium permanganate. *p*-Nitrobenzoic acid was thus obtained (m. p. and mixed m. p. 235—238°).

1-p-*Nitrophenoxy*-5-p-*nitrophenylpentane*.—A mixture of potassium *p*-nitrophenoxide (8 g.), crude 5-*p*-nitrophenylpentyl bromide (prepared by nitration of 6·6 g. of 5-phenylpentyl bromide at −25° to −40°), and 2-ethoxyethanol (20 ml.) was refluxed for 20 hr. The product, obtained as earlier described for the trinitro-compound, was chromatographed in benzene–light petroleum. Recrystallisation of the *product* (3·7 g., 39% overall; m. p. 55—58°) from methanol gave prisms, m. p. 69—71° (Found: N, 8·7. $C_{17}H_{18}O_5N_2$ requires N, 8·5%).

Chromatography of the crude nitro-compound revealed the presence of a small amount of an isomeric nitro-compound, presumably 1-p-*nitrophenoxy*-5-o-*nitrophenylpentane*. It crystallised from acetone–methanol in prisms, m. p. 81—82° (Found: N, 8·7%), depressed to 58—60° by the *p*-isomer.

TABLE 6. *Compounds* 

No.	X	R	Deriv.	Yield (%)		Solvent for recryst.
1	S·$[CH_2]_3$·S	H	Base	74·5 [a]	53—54°	EtOH
2			2HCl	59	255 [b]	Conc. HCl
3	O·$[CH_2]_3$·NH	H	Base	72	71	Aq. EtOH
4	NH·$[CH_2]_3$·NH	H	Base	62	110	EtOH–Pet [b]
5	NAc·$[CH_2]_3$·NAc	H	Base	96 [c]	193	Aq. EtOH
6	O·CO·$[CH_2]_3$·CO·O	H	Base	86	104—106	EtOAc–Et_2O
7	—	—	2Me·SO_3H	—	—	—
8	$[CH_2]_5$	H	Base	81 [d]	96—98	Pet [b]
9	—	—	2Me·SO_3H	—	212—215	EtOH–Et_2O
10	O·$[CH_2]_5$	NH_2	Base	62	107—110	$CHCl_3$–Et_2O

No.	Formula	Found (%) C	H	N	S	Required (%) C	H	N	S
1	$C_{15}H_{16}N_2S_2$	—	—	9·3	21·7	—	—	9·6	22·1
2	$C_{15}H_{16}N_2S_2$,2HCl	—	—	7·7	17·9	—	—	7·7	17·6
3	$C_{15}H_{15}ON_3$	70·0	7·7	16·2	—	70·0	7·4	16·3	—
4	$C_{15}H_{16}N_4$	70·4	8·0	21·6	—	70·3	7·8	21·9	—
5	$C_{19}H_{24}O_3N_4$	67·2	7·4	16·4	—	67·0	7·1	16·5	—
6	$C_{17}H_{18}O_4N_2$	65·2	6·0	8·8	—	65·0	5·8	8·9	—
7	$C_{17}H_{18}O_4N_2$,2CH_4O_3S	—	—	5·5	12·8	—	—	5·5	12·7
8	$C_{17}H_{22}N_2$	80·0	8·8	10·8	—	80·3	8·7	11·0	—
9	$C_{17}H_{22}N_2$,2CH_4O_3S	—	—	6·4	—	—	—	6·3	—
10	$C_{17}H_{23}ON_3$	—	—	15·0	—	—	—	14·7	—

[a] With decomp. [b] The dinitro-compound was reduced by the method of Waldron and Reid,[25] who describe the base as an oil. [b] Pet = light petroleum. [c] From the dinitro-compound.[18] [d] From 1 : 5-di-(*p*-nitrophenyl)penta-1 : 3-dien-5-one over Raney Ni in EtOAc.

Di-(p-*acetamidophenyl*) *Thiolsulphinate*.—A solution of monoperphthalic acid (3·12 g.) in ether (93 ml.) was added to a stirred solution of di-(*p*-acetamidophenyl) disulphide (4·9 g.) in acetone (300 ml.) at 0°. The solution was allowed to come to room temperature, kept for 1 hr.,

then filtered. The solid recrystallised from acetic acid, giving the *thiolsulphinate* (3·2 g.), m. p. 201° (decomp.) (Found: C, 55·15; H, 4·8; N, 8·1. $C_{16}H_{16}O_3N_2S_2$ requires C, 55·2; H, 4·6; N, 8·05%). A sample prepared by acetylation of di-(*p*-aminophenyl) thiolsulphinate had m. p. 207°.

Di-(p-*aminophenyl*) *Thiolsulphinate*.—Monoperphthalic acid (56 g.) in ether was added during 30 min. to a stirred solution of di-(*p*-aminophenyl) disulphide (76 g.) in ether (1·5 l.), the temperature being maintained below 0°. After a further 40 min., the solid was filtered off, dried in air, and stirred into saturated sodium acetate solution (1·5 l.). The solid was filtered off again and washed with water, ethanol and ether. Recrystallisation of the product (51 g.; m. p. 143—144°) was carried out by extracting it with four 300 ml. portions of pyridine at 60°; the extracts were diluted with two volumes of water at 60° and cooled, to give the *thiolsulphinate* (18·7 g., 23·5%), m. p. 153° (Found: C, 54·15; H, 4·85; N, 10·4; S, 23·6. $C_{12}H_{12}ON_2S_2$ requires C, 54·5; H, 4·55; N, 10·6; S, 24·2%).

3-p-*Aminoanilino*-1-p-*nitrophenoxypropane*.—3-*p*-Nitrophenoxypropyl bromide (10·4 g.), *p*-aminoacetanilide (5·44 g.), and potassium carbonate (5·4 g.) in acetone (100 ml.) were boiled under reflux for 24 hr. The hot mixture was filtered, then evaporated and the residue was boiled with 10% hydrochloric acid (100 ml.) for 30 min. The hot solution was treated with charcoal, filtered through Hyflo in a sintered-glass funnel, treated with an equal volume of concentrated hydrochloric acid, and cooled. The hydrochloride (5·5 g.) was filtered off and converted into the base. Crystallisation from ethanol gave 3-p-*aminoanilino*-1-p-*nitrophenoxypropane* (3·6 g., 31%), m. p. 148° (Found: C, 62·6; H, 6·05; N, 14·5. $C_{15}H_{17}O_3N_3$ requires C, 62·7; H, 5·9; N, 14·6%).

1 : 5-*Di*-(4-*nitro*-1-*naphthyloxy*)*pentane*.—1 : 5-Dibromopentane (11·5 g.) was added to a solution of 4-nitro-1-naphthol [32] (18·9 g.) and potassium hydroxide (5·6 g.) in 2-ethoxyethanol (150 ml.) and the mixture was refluxed for 4·5 hr., cooled, and filtered. Recrystallisation of the product (12·9 g., 58%; m. p. 148—152°) from aqueous dimethylformamide and from acetic acid gave yellow prisms, m. p. 155—157° (Found: N, 6·4. $C_{25}H_{22}O_6N_2$ requires N, 6·3%). Catalytic reduction yielded 1 : 5-di-(4-amino-1-naphthyloxy)pentane, isolated as the *dimethanesulphonate* (99%), m. p. 256—260° (Found: N, 4·9; S, 11·2. $C_{25}H_{26}O_2N_2,2CH_4O_3S$ requires N, 4·8; S, 11·05%).

1 : 5-*Di*-(4-*nitro*-4′-*diphenylyloxy*)*pentane*.—The potassium salt of 4-hydroxy-4′-nitrodiphenyl [33] (20·5 g.) was heated under reflux for 48 hr. with 1 : 5-dibromopentane (10 g.) in ethanol (400 ml.). The solution was poured into dilute aqueous sodium hydroxide, and the product was crystallised from acetic acid, giving 1 : 5-*di*-(4-*nitro*-4′-*diphenylyloxy*)*pentane* (13·35 g., 70%), m. p. 130—131° (Found: N, 5·6. $C_{29}H_{26}O_6N_2$ requires N, 5·6%). Catalytic reduction in ethyl acetate gave 1 : 5-*di*-(4-*amino*-4′-*diphenylyloxy*)*pentane* (85%), m. p. 169—171° (from aqueous pyridine) (Found: N, 6·35. $C_{29}H_{30}O_2N_2$ requires N, 6·3%).

Tetra-(p-*nitrophenoxymethyl*)*methane*.—A mixture of pentaerythritol bromide (7·76 g.), potassium *p*-nitrophenoxide (17·7 g.) and ethanol (40 ml.) was heated in a sealed tube at 170° for 20 hr. The combined products from four such experiments were recrystallised from dimethylformamide, giving the *product* (30·3 g., 61%), m. p. 274° (Found: N, 9·1. $C_{29}H_{24}O_{12}N_4$ requires N, 9·0%). Catalytic reduction over Raney nickel in dimethylformamide yielded *tetra*-(p-*aminophenoxymethyl*)*methane* (71%), m. p. 205—207° (from aqueous pyridine) (Found: C, 70·0; H, 6·4; N, 11·25. $C_{29}H_{32}O_4N_4$ requires C, 69·6; H, 6·4; N, 11·2%). The *tetramethanesulphonate*, recrystallised from ethanol, had m. p. 234—236° (Found: N, 6·3. $C_{29}H_{32}O_4N_4,4CH_4O_3S$ requires N, 6·3%).

The *amines* listed in Table 6 were obtained by catalytic reduction of the nitro-compounds.

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[32] Burkhardt and Wood, *J.*, 1929, 143.
[33] Jones and Chapman, *J.*, 1952, 1832.
[34] Reverdin and Dresel, *Ber.*, 1904, **37**, 4455.
[35] Waldron and Reid, *J. Amer. Chem. Soc.*, 1923, **45**, 2408.

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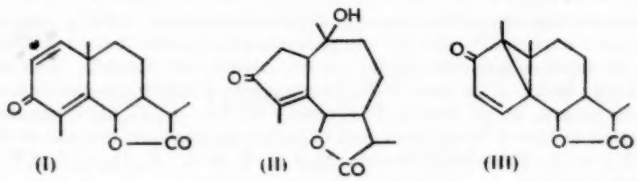
674. *Photochemical Transformations. Part V.* The Constitutions of Photosantonic Acid and Derivatives.*

By D. H. R. Barton, P. de Mayo, and M. Shafiq.

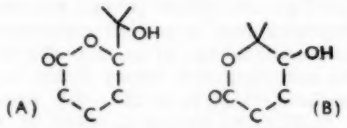
Experiments are described [1] which, when coupled with those of other workers, lead to the structure (XI; R = H) for photosantonic acid. The place of this acid in the pattern of the light-induced transformations of santonin is discussed, together with the nature of possible unstable intermediates.

In previous Parts of this series [2,3] the constitutions of two of the irradiation products of santonin (I), namely, *iso*photosantonic lactone (II) and lumisantonin [4] (III), have been established. Photosantonic acid, the photochemical transformation product of santonin which received the most attention from the earlier workers,[5] can be prepared by irradiation of santonin in aqueous acetic acid or in aqueous solution containing one equivalent of potassium hydroxide. The corresponding ester, photosantonin, was produced [5] by irradiation in ethanolic solution. It was believed to be a dibasic acid, but it has been shown [2] that the supposed dibasic acid is the solvated acid lactone: crystallisation from non-aqueous solvents gives the non-solvated form.



(I) (II) (III)

Photosantonin, $C_{17}H_{24}O_4$, contains an ethylenic linkage since, on titration with monoperphthalic acid, it consumes one atom of oxygen with formation of an epoxide. The environment of this double bond, in both photosantonin and in the derived hydroxy-acid ester, was shown by ozonolysis: acetone, characterised as its 2 : 4-dinitrophenylhydrazone, was obtained. The relation of this ethylenic linkage, now proved to be part of an *iso*propylidene grouping, to the carboxyl function in photosantonic acid was shown by a similar monoperphthalic acid oxidation. In place of the corresponding oxide a hydroxy-



(A) (B)

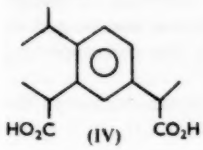
dilactone was obtained, derived by attack of the carboxyl group on the incipient epoxide. Since this substance exhibited bands in the infrared spectrum at 1755 (original γ-lactone) and 1735 (new lactone) cm.$^{-1}$, it must be a δ-lactone, whence two possibilities, A and B, for the partial structure of this hydroxy-dilactone follow. In a similar way bromination of photosantonic acid gave a bromo-lactone, also, since it had an infrared band at 1730 cm.$^{-1}$, to be formulated as a δ-lactone. This was reduced

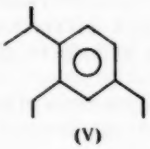
* Part IV, *J.*, 1958, 688.

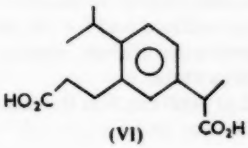
[1] For a preliminary communication, see Barton, de Mayo, and Shafiq, *Proc. Chem. Soc.*, 1957, 345.
[2] *Idem*, *J.*, 1957, 929.
[3] *Idem*, *J.*, 1958, 140.
[4] See also Arigoni, Bosshard, Bruderer, Büchi, and Krebaum, *Helv. Chim. Acta*, 1957, **40**, 1732; Cocker, Crowley, Edward, McMurry, and Stuart, *J.*, 1957, 3416.
[5] For summary see Simonsen and Barton, "The Terpenes," Vol. III, p. 292, Cambridge Univ. Press, 1952.

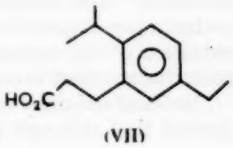
back to photosantonic acid with zinc and acetic acid, which regeneration precludes the possibility of rearrangement during the bromination.

The earlier Italian workers [5] found that passage of hydrogen chloride through an ethanolic solution of photosantonic acid and subsequent base-hydrolysis gave a mixture of optically active and racemic aromatic dicarboxylic acids which they formulated as (IV). By distillation from barium hydroxide, the racemic acid was converted into the hydrocarbon (V), the structure of which was convincingly established. However, the alternative structure (VI) for the dicarboxylic acid is in accord with its further degradation products, and in addition explains why, when photosantonic acid is heated with hydriodic acid to give pyrophotosantonic acid,[5] only one carboxyl group is lost [the pyro-acid would be (VII)].


(IV)

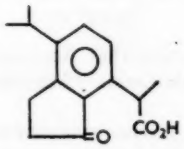

(V)

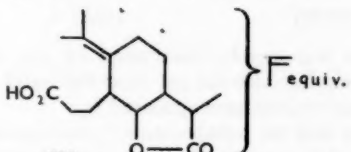

(VI)

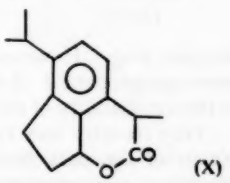

(VII)

Repetition of the preparation of the aromatic dicarboxylic acids followed by cyclisation in concentrated sulphuric acid gave an indanone (VIII), characterised as the methyl ester 2 : 4-dinitrophenylhydrazone. This demonstrates the correctness of formulæ (VI) and (VII).

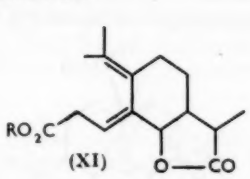
With this evidence the partial structure (IX) can be written for photosantonic acid, one

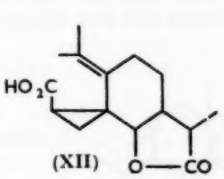

(VIII)

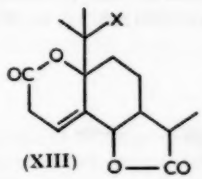

(IX)

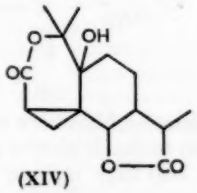

(X)

double-bond or ring remaining to be incorporated. In the latter case the proviso must be made that on treatment with hydrogen chloride the ring is cleaved with generation of a double-bond.


(XI)


(XII)


(XIII)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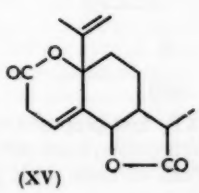
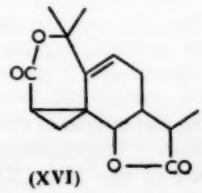

(XV)

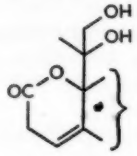

(XVI)

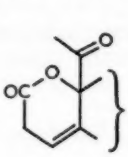
Support for (IX) was adduced as follows. First, the carboxyl group in (VIII) was shown to be δ to the ketonic function by reduction to the alcohol with potassium borohydride and cyclisation to the δ-lactone (X). Secondly, photosantonin and photosantonic

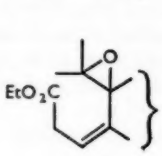
acid contain one methyl group less than santonin (Kuhn–Roth determination). Finally, oxidation with acidic permanganate solution gave succinic acid, in agreement with the presence of the grouping ·C·CH_2·CH_2·C·.

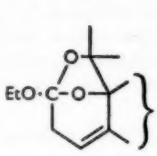
From this evidence, and from the fact that photosantonic acid is not an αβ-unsaturated acid, two structures (XI; R = H) or (XII), can be deduced. Correspondingly, (XIII; X = OH) or (XIV) will be then the hydroxy-lactone. By dehydration of the hydroxy-lactone with thionyl chloride and pyridine an anhydro-compound was obtained now to be formulated as (XV) or (XVI). Since the anhydro-compound did not show the intense band ($\varepsilon \sim 150$) near 890 cm.$^{-1}$ expected of an *iso*propenyl group as in (XV), because it did not give formaldehyde easily on ozonolysis, and because the bromo-lactone mentioned above is rather stable to ozone, the structure (XII) for photosantonic acid was initially favoured.[1] This formula adequately accounted for the ultraviolet spectrum of photosantonin (see Experimental section) and for the fact that this spectrum was unchanged on reduction of the compound with lithium aluminium hydride to give the corresponding triol, characterised as its triacetate.

No band was observed at 3050 cm.$^{-1}$ in the infrared spectrum of photosantonin or in the derived triol although this was to be expected [6] from the presence of a CH_2 in a *cyclo*-


(XVII)

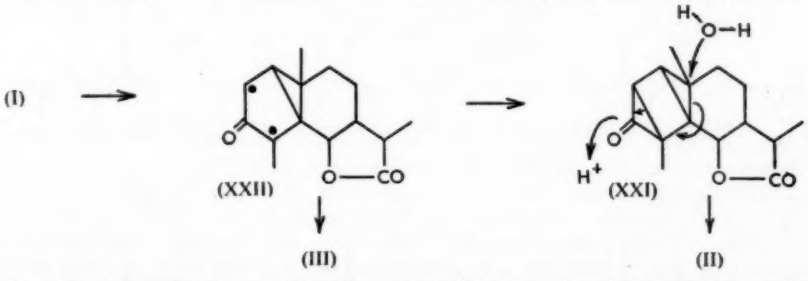

(XVIII)


(XIX)


(XX)

propane ring. However, this was largely discounted by the discovery that dimethyl *trans-cyclo*propane-1 : 2-dicarboxylate also did not show this band. Additional indications of the unreliability of this characteristic have appeared.[7]

Very recently van Tamelen and his collaborators [8] have provided further evidence in favour of the part structure (IX) and, in addition, on the basis of nuclear magnetic resonance measurements, have demonstrated the presence of a vinylic hydrogen in photosantonin. This strongly supports structure (XI). We have now found that the intensity of the 890 cm.$^{-1}$ band, characteristic of the *iso*propenyl group, is profoundly modified by the presence of an α-substituent. Thus 1 : 2-dimethylallyl benzoate has a band at 890 cm.$^{-1}$ (ε *ca.* 25) comparable with that of the anhydro-compound (about 27).*


(I) (XXII) (III) (XXI) (II)

The correctness of structure (XI), first proposed by van Tamelen,[8] has been confirmed as follows. Treatment of the anhydro-compound with osmium tetroxide gives a separable mixture of two diols (XVII). Both of these with periodic acid take up one atom of

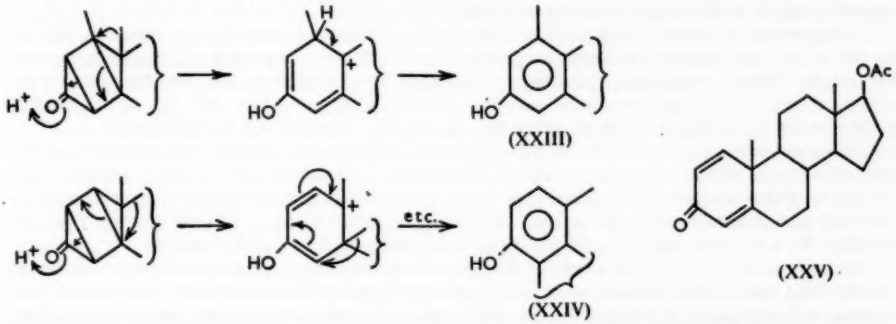
* We are grateful to Dr. E. S. Waight for his unpublished results.

[6] Cole, *J.*, 1954, 3807.
[7] Allen, Davis, Humphlett, and Stewart, *J. Org. Chem.*, 1957, **22**, 1291.
[8] van Tamelen, Levin, Brenner, Wolinsky, and Aldrich, *J. Amer. Chem. Soc.*, 1958, **80**, 501.

oxygen to give the same nor-ketone (XVIII). The alternative structure (XVI) would, of course, give a diketone without the loss of a carbon atom. The only evidence remaining against formula (XI; R = H) for photosantonic acid is its abnormal ultraviolet absorption spectrum. van Tamelen [8] has already commented on this and there is some analogy with 1 : 2-dimethylene*cyclo*hexane [9] to suggest that the spectrum of a compound like (XI; R = H) might be highly abnormal.

An interesting transformation product of photosantonin epoxide (XIX) was obtained on treatment with the boron–trifluoride ether complex. The product [10] showed no carbonyl band in the infrared spectrum other than that at 1778 cm.$^{-1}$ due to the γ-lactone, and is accordingly formulated as the orthoester (XX). In agreement with this, dissolution in aqueous ethanol containing hydrochloric acid rapidly converted it into the same hydroxy-dilactone (XIII; X = OH) obtained by the direct action of monoperphthalic acid on photosantonic acid (IX; R = H).

The existence of two routes for the photochemical conversion of santonin (I) into the lactone (II) has already been discussed.[3] There is a direct route, certainly operative for temperatures at or below room temperature, and an indirect route *via* lumisantonin (III)



which may be of some significance in refluxing aqueous acetic acid, although this is not obligatory. It is possible that there may be an unstable intermediate such as (XXI),[11] formed through (XXII), in the direct process. This, by the action of aqueous solvent, could be readily transformed, as indicated, into *iso*photosantonic lactone (II). Lumisantonin (III) might be derived from (XXII) by a simple redistribution of electrons.

It is of some interest that the intermediate (XXI) would account for the formation of phenols of both the *meta*- (as XXIII) and *para*-type (as XXIV) observed by Jeger and his collaborators [12] in the irradiation of the steroid (XXV).

Experimental

Unless specified to the contrary, $[\alpha]_D$ refer to $CHCl_3$ solutions; ultraviolet absorption spectra were determined, for EtOH solutions, on the Unicam S.P. 500 Spectrophotometer; infrared spectra refer to Nujol mulls unless otherwise indicated. Unless stated to the contrary, the light petroleum used was of b. p. 40—60°. M. p.s were determined on the Kofler block.

Photosantonin (XI; R = Et).—Santonin (12 g.) in ethanol (600 ml.) was irradiated in a Pyrex flask by means of a bare mercury arc (125 w), the process being followed by infrared spectroscopy. When the new peak in the carbonyl region (at 1736 cm.$^{-1}$) was stronger than all others in that region except that due to the γ-lactone the reaction was interrupted. Evaporation, chromatography on silica (450 g.), and elution with benzene–light petroleum (1 : 4), gave photosantonin (IX; R = Et) (4·8 g.), m. p. 67—68·5° (from carbon tetrachloride–light petroleum), $[\alpha]_D$ −121° (*c* 1·3 in EtOH), ε 8500 at 204 mμ (Found: *C*-Me, 14·6. Calc. for $C_{17}H_{24}O_4$: 3*C*-Me, 15·6%).

[9] Blomquist and Longone, *J. Amer. Chem. Soc.*, 1957, **79**, 3916.
[10] This compound has also been prepared by Professor G. Büchi (M.I.T.) (personal communication).
[11] Barton, *Proc. Chem. Soc.*, 1958, 61.
[12] Dutler, Bosshard, and Jeger, *Helv. Chim. Acta*, 1957, **40**, 494.

XUM

The ester (95 mg.) in ethanol (3 ml.) was shaken with 10% aqueous potassium carbonate (2 ml.) at room temperature for 24 hr. Isolation of the acidic fraction and crystallisation from ethanol–light petroleum gave the *hydroxy-dicarboxylic acid monoethyl ester*, m. p. 138—140°, $[\alpha]_D$ −24° (*c* 1·12) (Found: C, 65·6; H, 8·25; OEt, 15·05. $C_{17}H_{24}O_5$ requires C, 65·8; H, 8·45; 1OEt, 14·5%). Attempted acetylation of the hydroxy-acid re-formed photosantonin, identified by m. p., mixed m. p., and infrared spectrum.

Photosantonic Acid (XI; R = H).—A Kuhn–Roth determination gave *C*-Me 9·8% (Calc. for $C_{15}H_{20}O_4$: 2*C*-Me, 11·4%). Esterification of the acid (41·3 mg.) with ethereal diazomethane gave, after evaporation and crystallisation of the product from ether–light petroleum, the *methyl ester* (XI; R = Me), m. p. 54·5—55°, $[\alpha]_D$ −119° (*c* 0·85) (Found: C, 69·15; H, 8·05. $C_{16}H_{22}O_4$ requires C, 69·05; H, 7·95%).

Ozonolysis of Photosantonin.—The ester (70 mg.) in methylene dichloride (40 ml.) was ozonised at −60° for 20 min., after which there was no ultraviolet absorption in the 210 mμ region. Steam-distillation of the product into a solution of 2 : 4-dinitrophenylhydrazine in dilute sulphuric acid followed by isolation of the derivative and chromatography on bentonite–kieselguhr gave acetone 2 : 4-dinitrophenylhydrazone (14 mg., 23%), identified by m. p. and mixed m. p. (Found: C, 45·6; H, 4·4; N, 23·65. Calc. for $C_9H_{10}O_4N_4$: C, 45·4; H, 4·25; N, 23·5%). Under similar conditions the corresponding hydroxy-acid (see above) (72 mg.) also gave acetone 2 : 4-dinitrophenylhydrazone (13·5 mg., 24%).

Photosantonin Epoxide (XIX).—The ester (100 mg.) in ether (50 ml.) was treated with an excess (5 ml.) of ethereal 0·3N-monoperphthalic acid and kept overnight. Titration indicated an uptake of 0·97 atom-equiv. of oxygen. Isolation of the product and crystallisation from carbon tetrachloride–light petroleum gave the *epoxide* (XIX), m. p. 87—90°, $[\alpha]_D$ +10° (*c* 1·27), ε 4900 at 204 mμ (Found: C, 66·45; H, 7·65. $C_{17}H_{24}O_5$ requires C, 66·2; H, 7·85%).

Photosantonin Ethyl Orthoester (XX).—The epoxide (100 mg.) in ether (50 ml.) was treated with the boron trifluoride–ether complex (3 ml.) and kept for 4 min. at room temperature. Isolation of the product in the usual way and crystallisation from chloroform–light petroleum afforded the *orthoester* (XX), m. p. 167—169°, $[\alpha]_D$ +98° (*c* 1·03), ε 3100 at 204 mμ (Found: C, 66·0; H, 7·6; OEt, 14·5. $C_{17}H_{24}O_5$ requires C, 66·2; H, 7·85; 1OEt, 14·6%).

The orthoester (100 mg.) in alcohol (50 ml.) was treated with concentrated hydrochloric acid (5 ml.), and the mixture diluted with water (50 ml.). After 30 min. the mixture was further diluted and the product isolated in the usual way. Crystallisation from ethyl acetate–light petroleum then afforded the *hydroxy-dilactone* (XIII; X = OH), m. p. 172—175°, $[\alpha]_D$ +41° (*c* 1·53), ε 2300 at 204 mμ (Found: C, 64·25; H, 7·05. $C_{15}H_{20}O_5$ requires C, 64·25; H, 7·2%). The same substance was prepared in the following way. Photosantonic acid (128 mg.) in chloroform (50 ml.) was treated with ethereal 1·5N-monoperphthalic acid (2 ml.) and kept at room temperature overnight. Titration indicated the consumption of 1·06 atom-equivs. of oxygen. Isolation of the product in the usual way afforded the hydroxy-dilactone, identified by m. p., mixed m. p., rotation {$[\alpha]_D$ +41° (*c* 1·5)}, and infrared spectrum. The compound was recovered after attempted acetylation (acetic anhydride–pyridine) at room temperature overnight.

The Unsaturated Dilactone (XV).—The hydroxy-dilactone (XIII; X = OH) (50 mg.) in pyridine (3 ml.)w as treated with thionyl chloride (400 mg.) and kept at 0° for 15 min. Decomposition of the excess of acid chloride with water and isolation of the product in the usual way afforded the *anhydro-compound* (XV), m. p. 137—139°, $[\alpha]_D$ +88° (*c* 1·02), ε 3800 at 204 mμ (Found: C, 68·45; H, 6·95. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%). Ozonolysis, as described for photosantonin, and steam-distillation into a solution of dimedone did not afford formaldehyde dimethone.

Photosantonic Acid Bromo-lactone (XIII; X = Br).—Photosantonic acid (108 mg.) in chloroform (30 ml.) containing bromine (1·7 mol.) was kept for 2 min., titration then indicating the uptake of 1·1 mol. of bromine. Isolation of the product and crystallisation from chloroform–light petroleum afforded the *bromo-lactone* (XIII; X = Br) (81 mg.), m. p. 173—177° $[\alpha]_D$ +30° (*c* 1·46), ε 2400 at 204 mμ (Found: C, 52·55; H, 5·8; Br, 23·4. $C_{15}H_{19}O_4Br$ requires C, 52·5; H, 5·6; Br, 23·3%).

The bromo-lactone (21·7 mg.) in acetic acid (2 ml.) containing zinc dust (40 mg.) was refluxed for 4 hr. Isolation in the usual way afforded regenerated photosantonic acid, identified by m. p., mixed m. p., rotation {$[\alpha]_D$ −129° (*c* 1·0)}, and infrared spectrum.

Oxidation of Photosantonin.—Photosantonin (500 mg.), suspended in water (10 ml.), was treated dropwise with 5% aqueous potassium permanganate (135 ml.) on the steam-bath. At

the same time 8% sulphuric acid was added so that the solution remained faintly acidic during the oxidation. After removal of manganese salts and manganese dioxide the volume was reduced to 10 ml. and the residue continuously extracted with ether. Conversion of the material removed by the ether into the *p*-bromophenacyl derivative gave this ester of succinic acid, identified by m. p. (210—212°), mixed m. p., and analysis (Found: C, 46·9; H, 3·7; Br, 30·9. Calc. for $C_{30}H_{16}O_6Br_2$: C, 46·9; H, 3·15; Br, 31·2%). The acid itself was also isolated from the ether extract by crystallisation from ether–light petroleum and identified by m. p., mixed m. p., and infrared spectrum (KCl disc).

Cyclisation of the "Dehydrophotosantonic Acid."—Photosantonin (1 g.) in ethanol (20 ml.) was subjected to a stream of hydrogen chloride for 6 hr. at room temperature, the mixture then being left overnight. Isolation of the product followed by alkaline hydrolysis in aqueous ethanol gave acidic material. Chromatography of this on silica and elution with benzene–ether (25 : 1) gave a mixture of active and racemic " dehydrophotosantonic acids," m. p. 133—135°, $[\alpha]_D$ +18° (*c* 3·1 in EtOH). The acid mixture (140 mg.) was heated in concentrated sulphuric acid (3 ml.) on the steam-bath for 5 min. Isolation and chromatography of the product on silica (5 g.), and elution with benzene, gave 7-1'-*carboxyethyl*-4-iso*propylindan*-1-*one* (VIII), m. p. 111—112° (from ethyl acetate–light petroleum), $[\alpha]_D$ ±0° (*c* 1·2 in EtOH), $\lambda_{max.}$ 254 mμ (ε 8700), showing a broad infrared maximum at 1695 cm.$^{-1}$ (Found: C, 73·55; H, 7·7. $C_{15}H_{18}O_3$ requires C, 73·15; H, 7·35%). The indanone (60 mg.) was methylated with ethereal diazomethane and the product treated with 2 : 4-dinitrophenylhydrazine, to give the 2 : 4-*dinitrophenylhydrazone*, m. p. 104—107° (from ethyl acetate–light petroleum), $\lambda_{max.}$ 390 mμ (ε 35,000) (Found: C, 59·85; H, 5·55; N, 12·5. $C_{22}H_{24}O_6N_4$ requires C, 60·0; H, 5·5; N 12·70%).

Reduction of the Indanone (VIII).—The indanone (90 mg.) was set aside in ethanolic solution (3 ml.) containing potassium borohydride (200 mg.) for 10 min. Isolation of the product and crystallisation from chloroform–ether–light petroleum afforded the *indanol*, m. p. 119—124° (rapid heating) (Found: C, 72·85; H, 8·15. $C_{15}H_{20}O_3$ requires C, 72·55; H, 8·1%).

This alcohol (50 mg.) was heated at 130° for 1 hr. After separation into acidic and neutral material the neutral oil was sublimed at 150°/0·001 mm., to give the oily *lactone* (X) (Found: C, 78·0; H, 8·0. $C_{15}H_{18}O_2$ requires C, 78·25; H, 7·9%).

Reduction of Photosantonin by Lithium Aluminium Hydride.—Photosantonin (500 mg.) in ether (100 ml.) was treated with a solution of lithium aluminium hydride (1·5 g.) in ether (100 ml.). After 17 hr. the excess of reagent was decomposed; isolation in the usual way afforded the *triol*, m. p. 127·5—129·5° (from chloroform–light petroleum), $[\alpha]_D$ −69° (*c* 2·1), ε 9400, 6800, and 1400 at 208, 220, and 240 mμ respectively (Found: C, 70·65; H, 10·3. $C_{15}H_{24}O_3$ requires C, 70·85; H, 10·3%). The triol (89 mg.) in pyridine (3 ml.) was treated overnight at room temperature with acetic anhydride (3 ml.). The oily *triacetate* thus formed was purified by sublimation at 150°/0·001 mm. (Found: C, 66·6; H, 8·75. $C_{21}H_{32}O_6$ requires C, 66·3; H, 8·5%).

Preparation of the Nor-ketone (XVIII) (with O. C. Böckman).—The anhydro-compound (XV) (186 mg.) in dioxan (1·5 ml.) was added to a solution of osmium tetroxide (285 mg.) in dioxan (2 ml.) containing pyridine (3 drops). After 5 days the osmic ester was decomposed with hydrogen sulphide to give, after isolation in the usual way, by fractional crystallisation *diol-I*, m. p. 148—150° (from ethyl acetate–light petroleum), $[\alpha]_D$ +43° (*c* 0·77 in EtOH) (Found: C, 61·05; H, 7·0. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·8%), and *diol-II*, m. p. 220—225° (from ethyl acetate–ethanol), $[\alpha]_D$ +9° (*c* 0·74 in EtOH) (Found: C, 60·25; H, 6·9. $C_{15}H_{20}O_6,\frac{1}{2}C_2H_5OH$ requires C, 60·2; H, 7·25%).

In preliminary experiments both diols consumed one atom of oxygen on titration with periodic acid. The diol-I (25 mg.) in aqueous dioxan containing periodic acid (110 ml.; 0·035N) was allowed to stand 3 hr. Iisolation of the product gave the *nor-ketone* (XVIII), m. p. 97—98°, $[\alpha]_D$ +210° (*c* 1·1) (Found: C, 63·6; H, 6·15. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1%). The same compound was isolated by cleavage of diol-II.

We thank the Government Grants Committee of the Royal Society and Imperial Chemical Industries Limited for financial assistance. Dr. M. A. T. Rogers provided us with several specimens of *cyclo*propane carboxylic acids.

THE UNIVERSITY, GLASGOW, W.2.
IMPERIAL COLLEGE, S.W.7.

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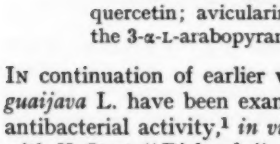
XUM

675. *Constituents of the Leaves of* Psidium guaijava, *L. Part II.* Quercetin, Avicularin, and Guaijaverin.*

By H. El Khadem and Y. S. Mohammed.

Three antibacterial compounds were isolated from guava leaves: quercetin; avicularin, the 3-L-arabofuranoside of quercetin; and guaijaverin, the 3-α-L-arabopyranoside of quercetin.

In continuation of earlier work (Part I) the active principles of the leaves of *Psidium guaijava* L. have been examined. The alcoholic extract and aqueous decoction showed antibacterial activity,[1] *in vitro* against *Staphylococcus aureus* and *in vivo* in mice infected with *H. Strep.* "Richards". Quercetin (I; R = R′ = H), avicularin, and another quercetin arabinoside (named guaijaverin) were isolated from the ethanolic extract of the defatted leaves. These three compounds inhibit the growth of *Staphylococcus aureus* at a dilution of 0·1 mg./ml., a value similar to that found previously for quercetin.[2] Avicularin, a 3-L-arabinoside of quercetin, was first isolated by Ohta[3] from *Polygonum aviculare* and was later found in *Vaccinium myrtillus*.[4] The structure assigned by Ohta has been confirmed and two new crystalline derivatives of avicularin have been prepared. Complete methylation with dimethyl sulphate and sodium hydroxide, followed by hydrolysis of the methylated glycoside, yielded 5 : 7 : 3′ : 4′-tetramethylquercetin (I; R = Me, R′ = H) and 2 : 3 : 5-tri-*O*-methylarabinose. The latter was converted by oxidation into 2 : 3 : 5-tri-*O*-methylarabonic acid, identified as its crystalline amide. It was concluded that arabinose was present in the furanose form so that avicularin would be the 3-L-arabofuranoside of quercetin.



(I)

Guaijaverin gave on hydrolysis quercetin and L-arabinose, the latter identified as the *N*-benzyl-*N*-phenylhydrazone. It was converted with diazomethane into a tetramethoxy-derivative which on hydrolysis yielded 5 : 7 : 3′ : 4′-tetramethoxyquercetin showing that, like avicularin, guaijaverin is a 3-L-arabinoside of quercetin. Complete methylation followed by hydrolysis yielded 5 : 7 : 3′ : 4′-tetramethylquercetin and 2 : 3 : 4-tri-*O*-methylarabinose, both crystalline, suggesting that the arabinose in guaijaverin is in the pyranose form. This was confirmed by synthesis; acetobromoarabinose was treated with 5 : 7 : 3′ : 4′-tetramethylquercetin and silver carbonate, according to Koenigs and Knorr's method,[5] giving 5 : 7 : 3′ : 4′-tetramethylguaijaverin triacetate, identical with that obtained by acetylation of tetramethylguaijaverin. The Koenigs–Knorr synthesis is known to produce the α-isomer in the case of L-arabinose,[6] so that guaijaverin would be the 3-α-L-arabopyranoside of quercetin.

The ultraviolet absorption maxima of avicularin, guaijaverin, and their acetates and methoxy-derivatives are shown in the Table.

Experimental

Absorption spectra were determined with a Unicam S.P. 500 spectrophotometer. Microanalyses are by A. Bernhardt, Mülheim, W. Germany.

Isolation of Crude Gum.—Powdered dried guava leaves (6·2 kg.) were defatted with light petroleum (b. p. 58—72°), then extracted with cold ethanol (4 × 8 l.). The green ethanol

* Part I, *J.*, 1952, 134.

[1] Bacteriological tests were made by Professor G. A. H. Buttle, School of Pharmacy, London, and continued by Dr. H. Mazloum, Faculty of Medicine, Alexandria University.

[2] Naghski, Copley, and Couch, *Science*, 1947, **105**, 125.

[3] Ohta, *Z. physiol. Chem.*, 1940, **263**, 221; *Ann. Report Tokyo Coll. Pharmacy*, 1955, **38**.

[4] Ice and Wender, *J. Amer. Chem. Soc.*, 1953, **75**, 50.

[5] Koenigs and Knorr, *Sitzb. Bayr. Akad. Wiss.*, 1900, **30**, 103; *Ber.*, 1901, **34**, 957.

[6] Pigman and Goepp, "Chemistry of the Carbohydrates," Academic Press Inc., New York, 1948, p. 103.

extracts were concentrated to 2 l., and hot water (1·5 l.) was added, giving a heavy green precipitate which was filtered off and washed repeatedly with hot water (290 g.). The combined filtrate and washings were concentrated under reduced pressure to about 0·5 l. and dried in a vacuum-desiccator, yielding a brown hygroscopic gum (150 g.).

Ether-extraction of the Crude Gum.—The brown gum (150 g.) was dissolved in water (500 ml.), filtered from a small insoluble residue, and subjected to continuous ether-extraction for 72 hr. The ether soon acquired a yellow tint and after 4 hr. started to deposit in the ether reservoir a crystalline yellow precipitate of crude avicularin, m. p. 195°, which was collected by decantation after being washed with ether (yield 5 g.). The ether-soluble material recovered on evaporation was a yellow gum which crystallised from dilute ethanol, giving quercetin (1·1 g.), m. p. and mixed m. p. 313°. Another yellow crystalline product was deposited in the bottom of the aqueous reservoir and was separated by filtration after being washed with dilute ethanol (3·2 g.). This product melted over a wide range (220—240°) and was found to be a mixture of guaijaverin and a potassium salt of quercetin.

Quercetin.—Apart from the ether-extract quercetin was obtained by boiling the crude gum (14 g.) with acetic acid (30 ml.), filtering the mixture, and adding water (20 ml.). This quercetin (120 mg.), purified by repeated crystallisation from dilute ethanol, also had m. p. and mixed m. p. 313° (Found: C, 59·9; H, 3·4. Calc. for $C_{15}H_{10}O_7$: C, 59·6; H, 3·3%).

Potassium Salt of Quercetin.—The product deposited in the aqueous reservoir of the ether-extractor was washed with dilute ethanol (3·2 g.) and boiled with ethanol (2 × 50 ml.), and the undissolved potassium salt of quercetin was filtered off and crystallised from water (yield, 1·1 g.). The ethanol filtrate, on concentration and addition of warm water, deposited guaijaverin, m. p. 235° (2·1 g.). The potassium salt (588 mg.) in boiling dilute hydrochloric acid precipitated quercetin which, crystallised (401 mg.) from dilute ethanol, had m. p. and mixed m. p. 313° (Found: C, 59·9, 59·9; H, 3·7, 3·6%). The mother-liquor after separation of quercetin was evaporated to dryness on the water-bath and the residue identified as potassium chloride.

Avicularin.—Crude avicularin obtained from the ether-extraction was repeatedly crystallised from dilute ethanol; it formed bright yellow needles, m. p. and mixed m. p. 217° (Found: C, 53·4; H, 4·3. Calc. for $C_{20}H_{18}O_{11},H_2O$: C, 53·1; H, 4·4%). On dehydration avicularin had m. p. 222°.

Hydrolysis. Avicularin (118 mg.) was hydrolysed with 3% sulphuric acid for 1 hr. at 100°; the deposited quercetin (80 mg.), crystallised from dilute ethanol, had m. p. and mixed m. p. 313° (Found: C, 59·9, 59·7; H, 3·4, 3·4. Calc. for $C_{15}H_{10}O_7$: C, 59·6; H, 3·3%). The hydrolysate after separation of quercetin was neutralised with barium carbonate, filtered, and passed through a cation-exchange resin. The colourless solution was evaporated to dryness, giving L-arabinose, m. p. 157°, $[\alpha]_D$ +98·5° (*c* 0·64 in H_2O). One-dimensional paper chromatograms of this product were run on Whatman No. 1 filter paper and developed with the upper layer of butan-1-ol–ethanol–water–ammonia (40 : 10 : 49 : 1). Spraying with 10% aqueous ammonium molybdate [7] and heating at 100° showed one spot, R_F 0·19; controls showed an identical value for L-arabinose. Another portion of arabinose from the hydrolysis was converted into the *N*-benzyl-*N*-phenylhydrazone, m. p. 173° alone or mixed with L-arabinose *N*-benzyl-*N*-phenylhydrazone.

Avicularin hepta-acetate. A solution of avicularin in dry pyridine was acetylated with acetic anhydride in the usual manner. The amorphous acetate obtained crystallised in one week and was purified by crystallisation from chloroform–light petroleum (b. p. 100—120°), forming colourless needles, m. p. 187°, $[\alpha]_D$ −136° (*c* 1·22 in $CHCl_3$). *Avicularin hepta-acetate* is soluble in chloroform or hot ethanol, and insoluble in light petroleum (Found: C, 56·1, 55·9; H, 4·5, 4·5. $C_{34}H_{32}O_{18}$ requires C, 56·0; H, 4·4%).

Tetra-O-methylavicularin. Avicularin (920 mg.), dissolved in methanol (50 ml.), was treated with 2% diazomethane in ether (150 ml.) and left to evaporate slowly at room temperature. After two days, the crystals that separated were filtered off and crystallised from chloroform–light petroleum (b. p. 100—120°) in colourless needles, m. p. 225°. *Tetra-O-methylavicularin* is soluble in chloroform or hot ethanol and insoluble in light petroleum (Found: C, 58·4; H, 5·2. $C_{24}H_{26}O_{11}$ requires C, 58·8; H, 5·3%).

Hydrolysis of tetramethylavicularin. A solution of tetra-*O*-methylavicularin (600 mg.) in hot ethanol (20 ml.) was refluxed with 3% sulphuric acid (20 ml.) on the water-bath for 2 hr.

[7] Spraying agent for reducing sugars: El Khadem and Hanessian, unpublished work.

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5 : 7 : 3′ : 4′-Tetramethoxyquercetin obtained was crystallised from ethanol (370 mg.), then having m. p. and mixed m. p. 194° (Found: C, 64·1, 64·0; H, 5·1, 5·2. Calc. for $C_{19}H_{18}O_7$: C, 63·7; H, 5·0%).

Complete methylation and hydrolysis of avicularin. A solution of avicularin hepta-acetate (1·1 g.) in acetone (200 ml.) was stirred with 35% aqueous sodium hydroxide (30 ml.). Dimethyl sulphate (10 ml.) was added during 2 hr. and the mixture heated to 80° to distil off acetone. The brown solution was then extracted with chloroform and the latter washed with water, dried, and evaporated, giving a brown gum of completely methylated avicularin. This was hydrolysed with 3% sulphuric acid for 3 hr. at 100°, giving 5 : 7 : 3′ : 4′-tetramethylquercetin, m. p. and mixed m. p. 194°.

The hydrolysate, after separation of tetramethylquercetin, was neutralised with barium carbonate, filtered, passed through a column of cation-exchange resin, and evaporated, giving a yellowish gum of methylated arabinose. This was oxidised with bromine water for 12 hr. at room temperature and excess of bromine removed by bubbling air through the solution. Hydrogen bromide was removed with silver carbonate and the filtrate passed through a cation-exchange resin. The acid obtained was distilled at 130°/6 mm., giving a colourless amorphous lactone, which was treated with ethanolic ammonia for 24 hr. at 0°. The amide obtained on evaporation crystallised from acetone, then having m. p. 140°, not depressed on admixture with 2 : 3 : 5-tri-*O*-methylarabonamide.

Guaijaverin.—Crude *guaijaverin* (2·1 g.) obtained after separation of the potassium salt of quercetin was purified by crystallisation from dilute ethanol in bright yellow needles, m. p. 239°, and, on dehydration, m. p. 256°. It is sparingly soluble in ethanol, methanol, and acetone (Found: C, 53·4; H, 4·7. $C_{20}H_{18}O_{11},H_2O$ requires C, 53·1; H, 4·4%).

Hydrolysis of guaijaverin. Guaijaverin (104 mg.) was hydrolysed with 3% sulphuric acid (20 ml.) for 1 hr. at 100° and the deposited quercetin (69 mg.) crystallised from dilute ethanol (m. p. and mixed m. p. 313°) (Found: C, 59·4, 59·6; H, 3·6, 3·6%).

The hydrolysate after separation of quercetin was neutralised with barium carbonate, filtered, and passed through a cation-exchange resin. The colourless solution was evaporated, giving L-arabinose, m. p. 157°, $[\alpha]_D$ +97·2° (*c* 0·55 in H_2O), identified as in the previous case.

Guaijaverin hepta-acetate. A solution of guaijaverin in dry pyridine was treated with acetic anhydride, and the *hepta-acetate* crystallised from chloroform–light petroleum (b. p. 100—120°) in colourless needles, m. p. 226°, $[\alpha]_D$ −102° (*c* 0·54 in $CHCl_3$) (Found: C, 56·2, 56·2; H, 4·6, 4·6. $C_{34}H_{32}O_{18}$ requires C, 56·0; H, 4·4%).

Tetra-O-methylguaijaverin. Guaijaverin (914 mg.) in methanol (50 ml.) was treated with 2% diazomethane in ether (150 ml.), and the mixture left to evaporate slowly at room temperature. After 2 days the crystals that separated were filtered off and crystallised from chloroform–light petroleum (b. p. 100—120°) in nearly colourless needles, m. p. 247°. *Tetra-O-methylguaijaverin* is soluble in chloroform, difficultly soluble in hot ethanol or methanol, and insoluble in light petroleum (Found: C, 59·2, 58·9; H, 5·4, 5·3; OMe, 24·8. $C_{24}H_{28}O_{11}$ requires C, 58·8; H, 5·3; OMe, 25·3%).

Hydrolysis of tetramethylguaijaverin. A solution of tetramethylguaijaverin (650 mg.) in hot ethanol (20 ml.) was refluxed with 3% sulphuric acid (20 ml.) on the water-bath for 2 hr. 5 : 7 : 3′ : 4′-Tetramethylquercetin obtained was crystallised from ethanol (yield, 420 mg.; m. p. and mixed m. p. 194°) (Found: C, 63·9; H, 5·1. Calc. for $C_{19}H_{18}O_7$: C, 63·7; H, 5·0%).

Tetra-O-methylguaijaverin triacetate. Tetramethylguaijaverin (60 mg.) in dry pyridine (2 ml.) was treated with acetic anhydride, and the *acetate* obtained crystallised from ether in needles, m. p. 159—160°, soluble in chloroform or hot ethanol, and insoluble in light petroleum (Found: C, 58·3, 58·5; H, 5·4, 5·3. $C_{30}H_{32}O_{14}$ requires C, 58·4; H, 5·2%).

Complete methylation and hydrolysis of guaijaverin. A solution of guaijaverin hepta-acetate (1·1 g.) in acetone (200 ml.) was treated with 35% aqueous sodium hydroxide (30 ml.) and dimethyl sulphate (10 ml.) as in the preceding case. The methylated guaijaverin was hydrolysed with 3% sulphuric acid (20 ml.) at 100° for 3 hr., giving 5 : 7 : 3′ : 4′-tetramethylquercetin, m. p. and mixed m. p. 194°; the liquor gave, as above, 2 : 3 : 4-tri-*O*-methylarabinose, m. p. and mixed m. p. 82°.

Synthesis of Tetra-O-methylguaijaverin Triacetate.—A solution of 5 : 7 : 3′ : 4′-tetramethylquercetin (30 mg.) and acetobromoarabinose (650 mg.) in dry benzene (25 ml.) was refluxed with silver carbonate (2 g.) for 2 hr., then filtered from the suspended silver salts. The clear solution was evaporated to dryness under reduced pressure and extracted with boiling ether (2 × 50 ml.);

and the ether extracts were filtered and concentrated to 5 ml. Colourless needles of 5 : 7 : 3′ : 4′-tetramethylguaijaverin triacetate separated and were crystallised from ether; they had m. p. and mixed m. p. 159—160°.

Absorption spectra.

Substance	Solvent	$\lambda_{max.}$ (mμ)	log ε	$\lambda_{min.}$ (mμ)	log ε
Avicularin	EtOH	260	4·32	235	4·07
		360	4·24	285	3·85
Avicularin hepta-acetate	,,	254	4·38	240	4·34
		307	4·33	280	4·08
Tetra-*O*-methylavicularin	$CHCl_3$	250	4·29	280	3·92
		335	4·24		
Guaijaverin	EtOH	260	4·45	235	4·19
		360	4·38	285	3·96
Guaijaverin hepta-acetate	,,	257	4·40	243	4·34
		311	4·38	280	4·15
Tetra-*O*-methylguaijaverin	$CHCl_3$	255	4·42	280	3·81
		345	4·34		

The authors thank Professor T. Ohta and Dr. C. W. Wilson for specimens, Professor E. El Shishiny and Dr. Callow, M.R.C., Mill Hill, for making available special apparatus, and Professors H. N. Rydon and G. Soliman for valuable discussions.

FACULTY OF SCIENCE, ALEXANDRIA UNIVERSITY,
ALEXANDRIA, EGYPT.

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676. *The Thermal Decomposition of Thallous Bromate.*

By JOHN SIMPSON, DUNCAN TAYLOR, and (in part) R. S. FANSHAWE, MISS J. M. NORBURY, and W. J. WATSON.

Thermal decomposition of thallous bromate *in vacuo* has been investigated at 120—165°, and the overall reaction found to be essentially $4TlBrO_3 \longrightarrow 2Tl_2O_3 + 2Br_2 + 3O_2$. In addition, a very small amount of thallous bromide was formed, and infrared absorption data for partially decomposed crystals suggested the formation of an intermediate product (of unknown constitution). The kinetics of the reaction, determined by oxygen pressure–time measurements, showed that the rapid evolution of a small quantity of gas by a first-order decay process, followed by a slow linear-rate reaction, preceded the main autocatalytic stage. The respective activation energies were determined. Intense ultraviolet irradiation *in vacuo* at room temperature changed the crystals from colourless to light brown, caused slight decomposition, and had a small effect on the kinetics of subsequent thermal decomposition. The mechanism and the effects of ageing and ultraviolet pre-irradiation are discussed.

THE kinetics of the thermal decomposition of thallous bromate have been found to resemble those of mercury fulminate [1] and lithium aluminium hydride [2] in that rapid evolution of a small quantity of gas followed by a slow linear-rate reaction precedes the main autocatalytic stage. Further, although the effects were much less pronounced than with fulminate, intense irradiation with ultraviolet light at room temperature caused slight decomposition and influenced the early stages of subsequent thermal decomposition. It was of interest therefore to see how far the mechanism could be interpreted in terms of reactions initiated at imperfections between the sub-grains of the crystals, a theoretical approach applied successfully by Bartlett, Tompkins, and Young to the fulminate decomposition [1,3] and by some of the present authors [4] to certain aspects of the

[1] Bartlett, Tompkins, and Young, *J.*, 1956, 3323.
[2] Garner and Haycock, *Proc. Roy. Soc.*, 1952, *A*, **211**, 335.
[3] Tompkins and Young, *Discuss. Faraday Soc.*, 1957, **23**, 202.
[4] Simpson, Taylor, and Anderson, *J.*, 1958, 2378.

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decomposition of ammonium dichromate. As in the latter investigation, kinetic experiments have been supplemented by infrared absorption measurements and microscopical observations.

Experimental

Thallous bromate was prepared by slow addition of potassium bromate (0·05 mole) in water (125 c.c.) to thallous nitrate (0·05 mole) in water (400 c.c.) at 70—80°, the precipitate being then brought completely into solution by heating almost to the b. p. The solid obtained by cooling overnight was recrystallised from water (400 c.c.) with slow cooling. The crystals, although small (0·1—0·3 mm.) and compact, showed numerous striæ and occasional dendritic growths, and unfortunately the habit was not improved by further crystallisations. Of two preparations, the first (referred to below as "aged") was stored in air in the dark in a closed weighing bottle for *ca.* 2 years before use; the second ("fresh") was used within a few weeks of its preparation.

The apparatus and experimental procedures were very similar to those previously described,[4,5] except that a thermostat-controlled Pirani gauge protected by liquid-nitrogen traps was added to the system. The gauge was calibrated with oxygen against the Macleod gauge. For experiments at 140—165°, the volume of the system (4350—6700 c.c.) was such that decomposition of 7—10 mg. of thallous bromate gave a final oxygen pressure not exceeding 0·1 mm., any bromine evolved being condensed in a liquid-nitrogen trap placed immediately after the reaction vessel. To study the initial stages of the reaction at 120—142°, 28—32 mg. were used in a volume of 936 c.c.; measurements were then terminated at oxygen pressures not greater than 0·08 mm. The reaction vessel's thermocouple, against which the platinum bucket containing the sample rested during the reaction, gave no indication of self-heating in any of the experiments. During ultraviolet irradiation (10 hr.) at a distance of 15 cm. from a 300 w Hanovia mercury lamp, crystals were spread in a thin layer in a vitreous silica tube. The tube was continuously evacuated with an oil-pump and occasionally shaken to expose fresh surfaces.

Results

Microscopical Observations.—When crystals were heated (2—3°/min.) in air on a hot-stage microscope, a number of irregularly shaped black nuclei appeared at 120—130°, and then increased in number and size in an indefinite manner with rising temperature until at 170—180° the crystals were completely black and showed numerous cracks and pits on the surfaces. Independently of the black nuclei, and separated from them, a number of red-brown patches also developed (140—150°) and these appeared to be within the crystals rather than on the surfaces. Black nuclei were often seen to grow through, but not to be initiated in, the brown areas. The same phenomena occurred when crystals were heated *in vacuo*, and both the brown and the black areas remained unchanged over several days if partially decomposed crystals were cooled to room temperature. It seems unlikely therefore that the brown areas were due solely to occluded bromine. In general, crystals appeared completely black after only 10—15% decomposition.

After ultraviolet irradiation, crystals were of a uniform light brown colour but otherwise unchanged in appearance under the microscope. The colour was stable both in dry air and *in vacuo*, but in moist air, over a period of several days, the colour gradually blackened and appreciable quantities of bromine were evolved. When heated, pre-irradiated crystals behaved in a manner very similar to that described above.

Chemistry of the Reaction.—The gaseous products of the reaction were shown to be oxygen and bromine and the black solid product to be mainly thallic oxide. Although a small amount of thallous bromide could be extracted from the solid product with hot water, the *X*-ray powder photograph showed only the spacings of Tl_2O_3. As calculated from the final pressure of non-condensable gas in the kinetics experiments at 140—165°, the quantity of oxygen evolved was 0·76 ± 0·04 mole per mole of thallous bromate and was independent of the temperature of decomposition or the age or pre-irradiation of the crystals. Decomposition of 0·25 g. samples at 150—155° in an evacuated tube attached to a liquid-nitrogen trap yielded 0·4 ± 0·05 mole

[5] Taylor, *J.*, 1955, 1033.

of bromine per mole. (Attempts to carry out bromine determinations with 0·45 g. samples at 170° were vitiated by minor explosions.) The overall reaction is thus essentially $4TlBrO_3 \longrightarrow 2Tl_2O_3 + 2Br_2 + 3O_2$, but with a further process occurring only to a small extent in which some of the bromine is retained in the solid product as thallous bromide. The loss in weight of samples in the kinetics experiments was 28 ± 3% compared with 31·3% required by the above equation.

Intense irradiation of crystals at room temperature in a quartz vessel attached to the thermal decomposition apparatus caused less than 0·3% of decomposition in 10 hr., as judged from the pressure of evolved oxygen. Traces of bromine were also evolved. When freshly irradiated crystals were crushed under a few drops of distilled water, the liquid gave a slight blue colour with starch–potassium iodide paper, indicating free bromine or some other oxidising agent.

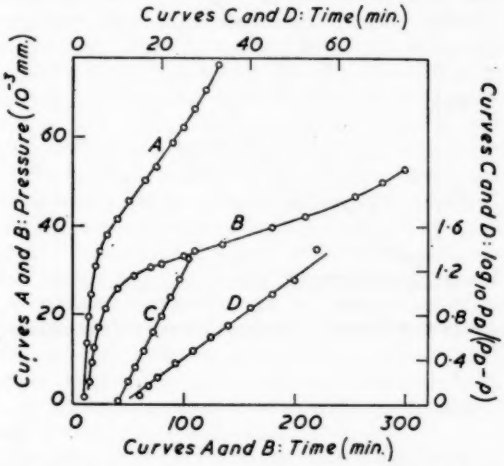

FIG. 1. *First-order decay and linear-rate processes for aged crystals.*
A and C: 135·5°, pre-irradiated.
B and D: 135·3°, un-irradiated.

It is significant that the same blue colour was obtained even after the irradiated crystals had been stored in a corked tube in air for three months.

In a search for intermediate products, infrared absorption measurements (KBr disc technique, Hilger H 800 spectrophotometer) were carried out on fresh thallous bromate and on samples which had been severally 11, 50, 81, and 100% decomposed at 160°. The relative intensities of the bromate ion peak [6] at 770 cm.$^{-1}$ showed that about 90% of the ions had disappeared by the time that only 60% of the possible oxygen had been evolved. Although the formation of an intermediate is thus indicated, and one from which oxygen is released on heating, the absence of new absorption peaks precluded its identification.

Kinetics of Oxygen Evolution.—The decomposition can be divided conveniently into three parts: (1) the two initial reactions terminating at between 3 and 7% decomposition, (2) the acceleration stage, which at 35—50% decomposition gives way to (3) the decay stage.

(1) *Initial reactions.* To avoid inconveniently high rates, the initial reactions had to be studied at 120—142° compared with 140—165° for the other two parts, but it is known qualitatively that the same essential features occur in both temperature ranges. For aged crystals, with or without pre-irradiation, Fig. 1 shows the two initial reactions to consist of (*a*) a rapid first-order decay process [7] given by the equation $\log_{10}[p_D/(p_D - p)] = kt$, where p_D is the pressure (mm.) at the conclusion of the process, followed by (*b*) a slow constant-area interface reaction terminating at pressure p_0 which corresponded to 3—4% decomposition. The values of p_D and p_0 were increased by pre-irradiation (cf. Fig. 1) but not appreciably by increase in decomposition temperature. The value of k at a given temperature was approximately doubled by pre-irradiation, while the linear rate increased about five-fold. The temperature coefficients of k and of the linear rate gave activation energies respectively of 35 ± 1·5 and

[6] Miller and Wilkins, *Analyt. Chem.*, 1952, **24**, 1253.
[7] For review of kinetic equations see Garner, "Chemistry of Solid State," Butterworths, London, 1955, p. 184.

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36 ± 4 kcal./mole, and neither value was changed by pre-irradiation. With fresh crystals, the initial reactions were very similar, except that the value of p_0 was higher than for aged crystals (corresponding to 5—7% decomposition), and tended to increase with increasing temperature.

(2) *Acceleration stage.* Irrespective of the age of crystals or the temperature (140—165°), the acceleration stage terminated at *ca.* 35% decomposition, and at *ca.* 50% after pre-irradiation. Figs. 2 and 3 show that the stage can be represented [7] by the Prout–Tompkins equation $\log_{10}$

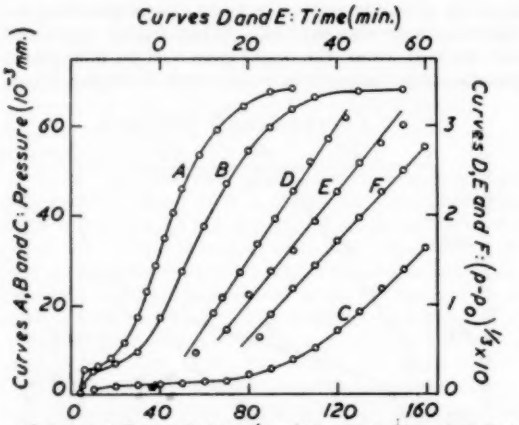

FIG. 2.

A and B: pressure–time plots for fresh crystals, with and without pre-irradiation respectively, A 160·5°, B 160·1°.

C: pressure–time plot for un-irradiated aged crystals, 151·6°.

D, E, and F: cube-law plots for curves A, B, and C respectively.

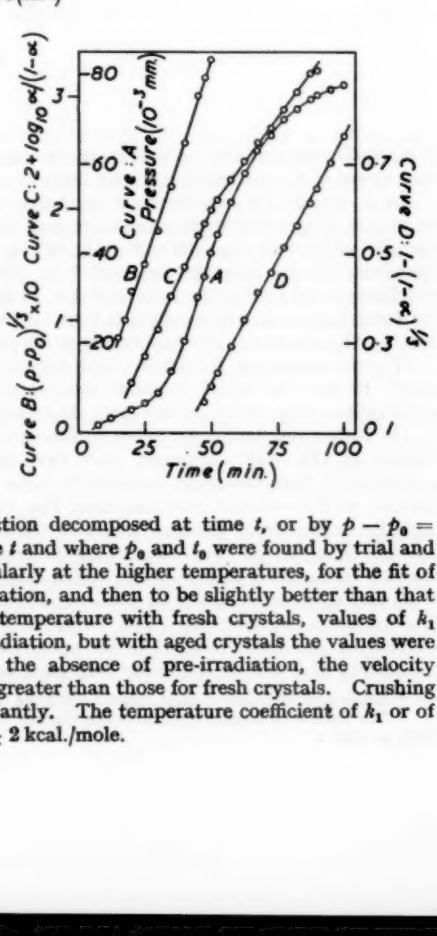

FIG. 3.

A: pressure–time plot for aged pre-irradiated crystals, 160°.

B, C, and D: cube-law, Prout–Tompkins, and contracting-sphere equation plots respectively for curve A.

$[\alpha/(1-\alpha)] = k_1 t +$ const., where α is the fraction decomposed at time t, or by $p - p_0 = k_2(t - t_0)^3$ where p is the pressure (mm.) at time t and where p_0 and t_0 were found by trial and error. There was, however, a tendency, particularly at the higher temperatures, for the fit of the cubic equation to be improved by pre-irradiation, and then to be slightly better than that of the Prout–Tompkins equation. At a given temperature with fresh crystals, values of k_1 and $k_2^{\frac{1}{3}}$ were increased by about 25% by pre-irradiation, but with aged crystals the values were either unchanged or tended to decrease. In the absence of pre-irradiation, the velocity constants for aged crystals tended to be slightly greater than those for fresh crystals. Crushing of the crystals did not affect the kinetics significantly. The temperature coefficient of k_1 or of $k_2^{\frac{1}{3}}$ always gave the same activation energy, 50 ± 2 kcal./mole.

(3) *Decay stage.* Fig. 3 is typical of the results obtained at 140—165° and showed that the stage is well represented [7] by the Prout–Tompkins equation, or by the contracting-sphere equation, $1 - (1 - \alpha)^{\frac{1}{3}} = k_3 t$. At a given temperature, the respective velocity constants were not changed significantly by ageing or pre-irradiation of the crystals, and their temperature coefficients gave the same activation energy, 35 ± 2 kcal./mole.

Discussion

Thallous bromate on ageing at room temperature does not change in appearance or undergo the slow decomposition which occurs with mercury fulminate, and it is therefore unlikely that the initial reactions involve merely desorption of gaseous products. The relatively high activation energy, *ca.* 35 kcal./mole, shows that the first-order decay and linear-rate processes both involve actual decomposition of the bromate. The processes (cf. mercury fulminate [1]) are consistent with (*a*) rapid decomposition at the sub-grain boundaries, the rate being determined at any given time by the fraction $(p_D - p)/p_D$ of available material, followed by (*b*) progression, for a short distance into the sub-grains, of a constant-area interface created during (*a*). Process (*b*) would correspond to the beginning of a contracting-envelope mechanism. Since pre-irradiation caused only slight decomposition of the solid, but increased the rates of (*a*) and (*b*) and also the value of p_0, its effect seems to be at least in part one of nucleation at and near sub-grain boundaries. Reaction (*a*) would then proceed from a larger number of centres and reaction (*b*) progress more rapidly and further into the body of the sub-grains. The higher values of p_0 for fresh than for aged crystals suggest that in the former a larger amount of disordered material is available at the boundaries so that decomposition occurs to a greater depth. Ageing would then be regarded as a type of annealing in which strain and disorder at the boundaries were relieved. It must be remembered, however, that the fresh and the aged crystals came from separate (but otherwise identical) preparations, and this may have caused part of the observed differences. Further, after aged crystals were recrystallised, an increase in p_0 occurred, but not quite up to the fresh-crystal value.

It is reasonable to assume that the above concept of the initial reactions is applicable in the higher temperature range where the main autocatalytic stage of the reaction was studied. Accordingly, it might be expected that crystals for which p_0 is relatively high would contain at the beginning of the acceleration a large number of non-contiguous crystal blocks, which may decompose in a manner analogous to the spherical growth of nuclei and have p–t^3 kinetics (cf. mercury fulminate [1]). However, as Fig. 3 shows for aged irradiated crystals, a clear decision between Prout–Tompkins and cubic-equation kinetics could not be made, and the same applied to fresh crystals. It was found, at most, that after pre-irradiation the cubic equation was in general slightly the more satisfactory, and then applied up to the maximum rate at *ca.* 50% decomposition as against *ca.* 35% for un-irradiated crystals. With fresh crystals after irradiation there was also a small increase in the acceleration velocity constants. At the conclusion of the initial reactions therefore the crystals may in fact consist of largely non-contiguous blocks whether pre-irradiated or not.

In the acceleration and decay stages, the activation energies, 50 and 35 kcal./mole respectively, both refer to linear growth, and since over a considerable fraction of the decomposition the corresponding rates do not differ by a factor of more than ten, the pre-exponential factor for the acceleration process must be 10^{6-7} greater than that for the decay process. This indicates that during the acceleration a single act of decomposition can trigger off the decomposition of a further considerable number of molecules, and/or that the reaction proceeds from a much greater number of reaction centres than the decay process. The occurrence of an intermediate, suggested by the infrared data, may be related to the above in that its formation may involve the higher activation energy and pre-exponential factor, and its decomposition the lower values.

A different interpretation of the decomposition mechanism (suggested to us by a

referee) may be derived on the assumption that the solid consists initially of a fixed number of isolated microcrystals, already nucleated, together with a number of larger, more perfect crystals. Random decomposition of the microcrystals by a linear-growth mechanism could then account for the initial reactions, the activation energy for linear growth being 35 kcal./mole, leading to an activation energy with respect to the extent of volume decomposition, α, of 3×35 kcal./mole. In the acceleration stage involving the more perfect crystals, one would expect that up to 10—15% of decomposition nuclei are being created and grow, and therefore that the kinetics in the simplest case would depend on t^4 and not t^3. By experiment, the p–t^3 relation is preferred, although in some of the runs a p–t^4 relation is almost as satisfactory. Nevertheless, the growth activation energy will now be 3×35 kcal./mole, so that the activation energy for nucleation would be about $(3 \times 50 - 3 \times 35) = 45$ kcal./mole. Nucleation on the more perfect crystals as a result of the initial reactions may not therefore be possible. The decay-stage activation energy, also 35 kcal./mole, again relates to a linear-growth process, so that consistency of activation energy values for the latter process is observed throughout the decomposition.

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CHEMISTRY DEPARTMENT, UNIVERSITY OF EDINBURGH. [*Received, April 8th,* 1958.]

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677. *Studies in the Vitamin D Field. Part III.* Approaches to Derivatives of 5-Hydroxy-2-methylcyclohexanone.*

By (the late) E. A. BRAUDE and A. A. WEBB, with (in part) M. U. S. SULTANBAWA.

Some reactions of 4-methyl*cyclo*hex-3-enol are described. Experiments on the addition of water, alcohols, etc., to the olefinic bond in 6-methyl*cyclo*hex-2-enone were successful (though in poor yield) only with benzyl alcohol. Some experiments on the synthesis of related intermediates are outlined.

IN connection with synthetical approaches to calciferol and its relatives,[1] protected derivatives (I) of 5-hydroxy-2-methyl*cyclo*hexanone were required; the methoxy-ketone (I; R = Me) has previously been prepared [2,3] by an eight-stage synthesis from *p*-cresol.

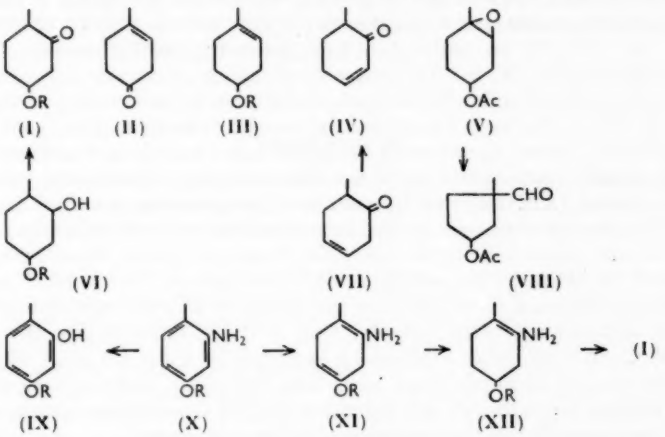
p-Methoxytoluene was reduced by lithium and ethanol in ether–liquid ammonia [3,4,5] to 4-methoxy-1-methyl*cyclo*hexa-1 : 4-diene, which was hydrolysed without purification to 4-methyl*cyclo*hex-3-enone (II) in 80% yield; this is a considerable improvement over that obtained by using sodium.[6,7] Reduction of the ketone (II) with lithium aluminium hydride gave the alcohol (III; R = H) which readily furnished the acetate (III; R = Ac) and the tetrahydropyranyl ether.[3] This acetate has previously been prepared [3,8] by a different route, but the present method is more convenient. Attempts to transform the double bond in the alcohol (III; R = H) directly into the $>CH{\cdot}CO^-$ grouping by reaction with performic acid [9] gave only 6-methyl*cyclo*hex-2-enone (IV). Reaction of the acetate (III; R = Ac) with monoperphthalic acid readily furnished the epoxide (V), the

* Part II, Braude and Wheeler, *J.*, 1955, 329.

[1] Braude and Wheeler, *J.*, 1955, 320.
[2] U.S.P. 2,511,815; G.P. 800,573; *Chem. Abs.*, 1950, **44**, 9981; 1951, **45**, 1624; cf. Corsano and Capitò, *Gazzetta*, 1955, **85**, 1590.
[3] Inhoffen, Weissermel, and Quinkert, *Chem. Ber.*, 1955, **88**, 1313.
[4] Wilds and Nelson, *J. Amer. Chem. Soc.*, 1953, **75**, 5360, 5366.
[5] Soffer and Jevnik, *ibid.*, 1955, **77**, 1003.
[6] Birch, *J.*, 1944, 430.
[7] *Idem*, *J.*, 1946, 593.
[8] Jones and Sondheimer, *J.*, 1949, 615.
[9] Cf. Mousseron, Jacquier, and Christol, *Compt. rend.*, 1953, **238**, 927.

preparation of which was described by Inhoffen [3] after this part of the investigation was completed. Isomerisation of the epoxide by mineral acids [10,11] or by boron trifluoride [11,12] was accompanied by loss of acetic acid, and again 6-methyl*cyclo*hex-2-enone (IV) was formed.

The epoxide was isomerised by magnesium bromide in boiling ether [13,14] to a carbonyl



compound, which gave a yellow 2 : 4-dinitrophenylhydrazone, m. p. 140°, prepared under acidic conditions and exhibiting light-absorption properties ($\lambda_{max.}$ 3600 Å) characteristic of the derivative of a saturated aldehyde or ketone. This stability towards acid, however, was clearly incompatible with the desired structure (I; R = Ac), and as it gave a positive Schiff test, and reduced Fehling's solution it is formulated as 3-acetoxy-1-methyl*cyclo*pentylformaldehyde (VIII); a similar acid-catalysed rearrangement, of 1 : 2-epoxymethyl*cyclo*hexane to 1-methyl*cyclo*pentylformaldehyde, has long been known.[15] The aldehyde showed only a single carbonyl absorption band in the infrared spectrum, at 1739 cm.$^{-1}$, but this was of very high intensity, evidently owing to the combined effect of the aldehyde group and the acetate-carbonyl group.

The course of isomerisation of the epoxide is highly dependent on the conditions used. Conversion into the *cyclo*pentane system (VIII) is best effected by the use of magnesium bromide prepared from the metal and purified ethylene dibromide.[14] When the salt was prepared from its elements [16] the isomerisation products contained variable proportions of 6-methyl*cyclo*hex-2-enone (IV); in one experiment a bromohydrin was obtained. Replacement of magnesium bromide with zinc chloride, reported [17] to be highly effective in the isomerisation of aliphatic epoxides to ketones, gave only unchanged starting material.

Although it is clear that the β-hydroxy-ketone (I; R = H) and its derivatives readily

[10] Cf. Maclean, Silverstone, and Spring, *J.*, 1951, 935; Elks, Evans, Oughton, and Thomas, *J.*, 1954, 463.

[11] Schoenwaldt, Turnbull, Chamberlin, Rheinhold, Erickson, Ruyle, Chemerda, and Tishler, *J. Amer. Chem. Soc.*, 1952, **74**, 2696.

[12] Bladon, Henbest, Jones, Lovell, Wood, Woods, Elks, Evans, Hathway, Oughton, and Thomas, *J.*, 1953, 2921; Heusler, Heusser, and Anliker, *Helv. Chim. Acta*, 1953, **36**, 398; Grigor, Laird, Maclean, Newbold, and Spring, *J.*, 1954, 2333; Inhoffen and Mengel, *Chem. Ber.*, 1954, **87**, 146.

[13] Tschoubar, *Compt. rend.*, 1942, **214**, 117; Gaylord and Becker, *Chem. Rev.*, 1951, **49**, 413; Bachmann, Horwitz, and Warzynski, *J. Amer. Chem. Soc.*, 1953, **75**, 3268.

[14] Stevens and Dykstra, *ibid.*, 1954, **76**, 4402.

[15] Tiffeneau, *Compt. rend.*, 1932, **195**, 1284; cf. Naqvi, Horwitz, and Filler, *J. Amer. Chem. Soc.*, 1957, **79**, 6283.

[16] Rowley, *J. Amer. Chem. Soc.*, 1950, **72**, 3305.

[17] Gasson, Graham, Millidge, Robson, Webster, Wild, and Young, *J.*, 1945, 2170.

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undergo conversion into the ethylenic ketone (IV) such reactions are usually measurably reversible. 6-Methyl*cyclo*hex-3-enone (VII) was therefore prepared by reduction of *o*-methoxytoluene with lithium and ethanol under essentially the same conditions as for the *para*-isomer, and it was converted into the conjugated compound (IV) by hot dilute sulphuric acid. The attempted additions to this of acetic acid, formic acid, and hydrogen bromide were fruitless, but with benzyl alcohol, which reacts favourably in related cases,[18] and with boron trifluoride–mercuric oxide as catalyst, a small amount of the benzyloxy-ketone (I; R = CH_2Ph) was isolated as its 2 : 4-dinitrophenylhydrazone. A solution of the unsaturated ketone (IV) in 0·1N-methanolic potassium hydroxide showed at room temperature (and rapidly when heated) a steady diminution in the intensity of the absorption maximum at 2260 Å, but only the original ketone and resinous material could be isolated from the product; several variations in conditions failed to yield any methoxy-compound.

Another possible route to ketones (I) is a Birch reduction of the amino-ether (X) to the dihydro-compound (XI), followed by selective hydrogenation to the tetrahydro-compound (XII) and acid hydrolysis to (I). In a model experiment, *o*-toluidine was reduced with lithium and ethanol in liquid ammonia,[19] and the crude dihydro-compound was hydrogenated in ethanol–ether–acetic acid; hydrolysis of the product gave mainly 2-methyl*cyclo*hexanone, thus establishing the feasibility of the route, but application of the method to 2-amino-4-methoxytoluene (X; R = Me) failed to give any of the ether (I; R = Me). In some other exploratory experiments, reduction of *o*- and *p*-anisidine with lithium–ethanol–ammonia gave, after acid hydrolysis, *cyclo*hex-2-enone and *cyclo*hexane-1 : 4-dione respectively; reductive removal of the methoxy-group, as observed in certain other cases,[20] had thus occurred with the *ortho*-isomer.

A method described [2,3] for the preparation of the methyl ether (I; R = Me) is by oxidation of 5-methoxy-2-methyl*cyclo*hexanol (VI; R = Me), but the preparation of the latter involves a lengthy series of reactions. Investigations were therefore made of other possible routes to compounds of type (VI) or suitable precursors. Clemmensen reduction of 2 : 4-dihydroxybenzaldehyde has been reported to be unsatisfactory,[21] and we found no improvement by the use of variations recommended [22] in other difficult cases. Wolff–Kishner reduction of the aldehyde has not been reported (though 2 : 4-dimethoxybenzaldehyde is quite readily reduced [23]) but again we obtained no 4-methylresorcinol under a variety of conditions. This is probably due to the fact that even with an excess of hydrazine the aldehyde gives the azine rather than the hydrazone, and although azines have been used for Wolff–Kishner reductions this one appears to be exceptionally stable; it was isolated from the reaction products on several occasions. Catalytic hydrogenation of 2 : 4-dihydroxybenzaldehyde over platinum is known [21] to give a small yield of 4-methylresorcinol but it has now been found that hydrogenation in methanol over highly active Raney nickel gives an excellent yield of 4-methyl*cyclo*hexane-1 : 3-diol (VI; R = H), probably as a mixture of stereoisomers; benzoylation under controlled conditions gave a product which, although non-crystalline, was a monobenzoate as shown by analysis and infrared spectrum. On oxidation with chromic acid it gave a product which furnished the 2 : 4-dinitrophenylhydrazone of 6-methyl*cyclo*hex-2-enone (IV); benzoylation had therefore occurred in the 1-position to give (VI; R = Bz), but the usual elimination had taken place under the acidic oxidation conditions.

The monobenzoylation of 2 : 4-dihydroxybenzaldehyde was described by Leon and Robinson,[24] who obtained the 4-monobenzoate, in unstated yield, as the chief product.

[18] Hoffman, *J. Amer. Chem. Soc.*, 1927, **49**, 530; Hirschmann, Hirschmann, and Daus, *ibid.*, 1952, **74**, 539; Bernstein, Heller, and Stolar, *ibid.*, 1954, **76**, 5674.
[19] Stork and White, *ibid.*, 1956, **78**, 4604.
[20] Birch, *J.*, 1947, 102.
[21] Bell, Bridge, and Robertson, *J.*, 1937, 1542.
[22] Robinson and Shah, *J.*, 1934, 1491; Steiger and Reichstein, *Helv. Chim. Acta*, 1938, **21**, 161.
[23] Cram, *J. Amer. Chem. Soc.*, 1948, **70**, 4240.
[24] Leon and Robinson, *J.*, 1931, 2732.

A detailed reinvestigation of this reaction has now shown that a considerable proportion of the 2-monobenzoate is also formed. Hydrogenation of the 4-monobenzoate over Raney nickel in ether gave a small yield of a solid, the analysis and infrared spectrum of which were compatible with its formulation as 3-hydroxy-4-methyl*cyclo*hexyl benzoate (VI; R = Bz).

Reduction of the acetate or benzoate of 4-methyl-3-nitrophenol gave the corresponding *O*-derivative (X; R = Ac or Bz) of the aminophenol; diazotisation of this *O*-benzoate gave 3-hydroxy-4-methylphenyl benzoate (IX; R = Bz).

Experimental

In this and the following paper, analyses were by Mr. F. H. Oliver, Miss J. Cuckney and their staff, and absorption spectra by Mr. R. L. Erskine, B.Sc., A.R.C.S., and Mrs. A. I. Boston.

Unless otherwise stated, 2 : 4-dinitrophenylhydrazones were chromatographed on alumina in benzene.

4-*Methyl*cyclo*hex*-3-*enone*.—*p*-Methoxytoluene (122 g., 1 mol.) was added to a stirred mixture of anhydrous ether (600 ml.) and liquid ammonia (1·6 l.). After 15 min., lithium (26·4 g., 3·8 equiv.) was added in small strips (0·1 g.) during 30 min. Stirring was continued for 15 min. and then dry ethanol (193 g., 4·2 mol.) was added dropwise during 30 min. Stirring was continued until the blue colour of the solution had been discharged (*ca.* 1 hr.) and most of the ammonia was then allowed to evaporate. Ice (750 g.) was added to the residue, which was then extracted with ether. The ether layer was washed with water, concentrated to about 250 ml. under reduced pressure, and stirred overnight with aqueous 2M-oxalic acid (250 ml.). The ether layer was again separated, combined with ether extracts of the aqueous layer, washed with sodium hydrogen carbonate solution and water, dried (Na_2SO_4), and distilled, giving 4-methyl*cyclo*hex-3-enone (88 g., 80%), b. p. 36°/4 mm., n_D^{21} 1·4693, $\lambda_{max.}$ (in EtOH) 2800 Å (ε 24) (Found: C, 76·1; H, 9·5. Calc. for $C_7H_{10}O$: C, 76·3; H, 9·15%) (lit.,[7] b. p. 74°/17 mm.). The 2 : 4-dinitrophenylhydrazone, prepared in ethanol–phosphoric acid,[25] crystallised from aqueous ethanol in orange prisms, m. p. 119—121°, $\lambda_{max.}$ (in EtOH) 3650 Å (ε 22,600) (lit.,[7] m. p. 120—121°, $\lambda_{max.}$ 3680 Å, ε 20,200).

4-*Methyl*cyclo*hex*-3-*enol*.—The foregoing ketone (82 g., 0·74 mol.) in ether (300 ml.) was added dropwise during 1·5 hr. to a stirred solution of lithium aluminium hydride (16 g., 0·42 mol.) in ether (300 ml.) heated under reflux. Heating and stirring were continued for a further 2·5 hr., then excess of 10% hydrochloric acid was added to the cooled mixture; the ether layer was separated and combined with the ether extracts of the aqueous layer, washed with water, dried (Na_2SO_4), and distilled giving 4-methyl*cyclo*hex-3-enol (75 g., 90%), b. p. 61—62°/5 mm., n_D^{24} 1·4810, $\nu_{max.}$ (liquid film) 3330 (OH), 1669 (C=C) cm.$^{-1}$ (lit.,[3] b. p. 89°/26 mm., n_D^{22} 1·4803). The 3 : 5-dinitrobenzoate crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 115—116° (Found: C, 54·9; H, 4·8; N, 9·3. Calc. for $C_{14}H_{14}O_6N_2$: C, 54·9; H, 4·6; N, 9·15%) (lit.,[3,8] m. p. 113—113·5°, 107°). The α-*naphthylurethane* crystallised from benzene–light petroleum (b. p. 60—80°) in needles, m. p. 146—147° (Found: C, 76·5; H, 6·9; N, 5·1. $C_{18}H_{19}O_2N$ requires C, 76·8; H, 6·8; N, 5·0%).

Reaction of 4-*Methyl*cyclo*hex*-3-*enol with Performic Acid*.—The alcohol (3·4 g.) was dissolved in 98% formic acid (15 ml.), and 30% hydrogen peroxide (10 ml.) was added, followed by two drops of concentrated sulphuric acid. The solution was stirred for 2 hr. at 40—45° and became green. Sulphuric acid (7 ml.) was added to the cooled solution and stirring was continued for 2 hr. at room temperature. Isolation of the product with ether and treatment with Brady's reagent gave the 2 : 4-dinitrophenylhydrazone (form *A*) of 6-methyl*cyclo*hex-2-enone, m. p. and mixed m. p. 125—126°. (Two forms, m. p.s 122—125·5° and 162—164°, are known.[24])

4-*Methyl*cyclo*hex*-3-*enyl Tetrahydropyran*-2-*yl Ether*.—Freshly distilled 2 : 3-dihydro-4*H*-pyran (20·5 g.) was added to a solution of 4-methyl*cyclo*hex-3-enol (5·5 g.) in ether (50 ml.), followed by phosphorus oxychloride (0·3 ml.). After 12 hr. at room temperature, solid potassium hydroxide (5 g.) was added and after a further 48 hr. the mixture was filtered and

[25] Johnson, *J. Amer. Chem. Soc.*, 1951, **73**, 5888.
[24] Yanagita, Inayama, and Kitagawa, *J. Org. Chem.*, 1956, **21**, 612.

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distilled, giving the ether (6·2 g., 65%), b. p. 77—79°/0·2 mm., n_D^{22} 1·4740 (Found: C, 73·5; H, 10·5. Calc. for $C_{12}H_{20}O_2$: C, 73·4; H, 10·3%) (lit.,[3] b. p. 90—91·5°/3 mm.).

4-*Acetoxy*-1-*methyl*cyclo*hexene*.—Acetyl chloride (42 g.) in benzene (100 ml.) was added dropwise during 1 hr. to a stirred solution of 4-methyl*cyclo*hex-3-enol (57 g.) in light petroleum (b. p. 40—60°) (200 ml.) and pyridine (45 g.) at −10° to 0°. Stirring was continued for 30 min. and the mixture was then kept at room temperature for 24 hr. The pyridine hydrochloride was filtered off and washed with light petroleum, and the combined filtrates were washed with 2N-hydrochloric acid and water, dried (Na_2SO_4), and distilled, giving 4-acetoxy-1-methyl*cyclo*hexene (64 g., 82%), b. p. 64—65°/5 mm., n_D^{18} 1·4591, $\nu_{max.}$ (liquid film) 1735 (C=O), 1677 (C=C), and 1245 (C–O in acetate) cm.$^{-1}$ (lit.,[3,8] b. p. 90°/23 mm., n_D^{24} 1·4548).

4-*Acetoxy*-1 : 2-*epoxy*-1-*methyl*cyclo*hexane*.—The foregoing acetate (13·5 g.) in ether (20 ml.) was added to a solution (200 ml.; 14% w/v) of monoperphthalic acid in ether at 0°. After 1 hr., the mixture was allowed to attain room temperature and kept for 24 hr. The precipitate of phthalic acid was filtered off and the solution was washed with sodium hydrogen carbonate and water, dried (Na_2SO_4), and distilled, giving the epoxide as a sweet-smelling liquid (9·6 g., 64%), b. p. 85—87°/4 mm., n_D^{23} 1·4528, $\nu_{max.}$ (liquid film) 1736 (C=O), 1244 (C–O in acetate), 1212, 848, and 835 (epoxide?) cm.$^{-1}$ (Found: C, 63·5; H, 8·4. Calc. for $C_9H_{14}O_3$: C, 63·5; H, 8·3%) (lit.,[3] b. p. 113—119°/24 mm.).

Treatment of the epoxide (1 ml.) with 2 : 4-dinitrophenylhydrazine (1 g.) in concentrated hydrochloric acid (30 ml.), water (30 ml.), and ethanol (5 ml.) gave very little precipitate at room temperature, but after 10 min. at 90° a red oil separated which after chromatography furnished 6-methyl*cyclo*hex-2-enone 2 : 4-dinitrophenylhydrazone (form *A*) (0·25 g.), m. p. and mixed m. p. 124—126°.

Treatment of the epoxide (1 ml.) with boron trifluoride–ether complex (1 ml.) in ether (10 ml.) for 72 hr. at 5—10°, followed by addition of aqueous sodium hydrogen carbonate, isolation of the product with ether, and reaction with 2 : 4-dinitrophenylhydrazine in 5N-hydrochloric acid, also gave the derivative of 6-methyl*cyclo*hex-2-enone, m. p. and mixed m. p. 125—126° (form *A*), $\lambda_{max.}$ (in EtOH) 3800 Å (ε 28,500) (Found: C, 54·2; H, 5·1; N, 19·3. Calc. for $C_{13}H_{14}O_4N_4$: C, 53·8; H, 4·9; N, 19·3%) (lit.,[26] m. p. 122—125·5°).

When the epoxide (1·0 g.) was treated for 24 hr. at room temperature with 2 : 4-dinitrophenylhydrazine (5 g.) and sulphuric acid (10 ml.) in methanol (75 ml.) it gave 5-(2 : 4-dinitrophenylhydrazino)-2-methyl*cyclo*hexanone 2 : 4-dinitrophenylhydrazone, orange plates (from pyridine–methanol), m. p. and mixed m. p. 187—188° (decomp.), $\lambda_{max.}$ (in EtOH) 3500 Å (ε 36,600) (lit.,[7] m. p. 176—177°).

3-*Acetoxy*-1-*methyl*cyclo*pentylformaldehyde*.—Freshly distilled ethylene dibromide (6 g.) was added to dry magnesium turnings (3 g.) in ether (50 ml.) and when the vigorous reaction had subsided the mixture was refluxed for 15 min., then cooled to 0°. On addition of the foregoing epoxide (5 g.) a copious flocculent white precipitate of the epoxide–magnesium bromide complex was formed immediately. The mixture was heated under gentle reflux for 60 hr. Water was then added and the ether layer was separated, combined with ether extracts of the aqueous layer, washed with water, dried (Na_2SO_4), and distilled, giving a main fraction (3·3 g.), which on redistillation furnished 3-*acetoxy*-1-*methyl*cyclo*pentylformaldehyde* (0·75 g.), b. p. 61—64°/0·1 mm., n_D^{23} 1·4518, $\lambda_{max.}$ (in EtOH) 2720 Å (ε 12), $\nu_{max.}$ (in CCl_4) 2778 and 2703 (C–H in CHO), 1739 (C=O in aldehyde and in acetate), 1242 (C–O in acetate) cm.$^{-1}$ (Found: C, 63·6; H, 8·7. $C_9H_{14}O_3$ requires C, 63·5; H, 8·3%). It gave a positive test with Schiff's reagent, and reduced boiling Fehling's solution. The 2 : 4-*dinitrophenylhydrazone*, prepared in ethanol–phosphoric acid, was chromatographed and then crystallised from aqueous methanol in yellow plates, m. p. 139—141°, $\lambda_{max.}$ (in $CHCl_3$) 3600 Å (ε 23,000) (Found: C, 51·65; H, 5·4; N, 16·1. $C_{15}H_{18}O_6N_4$ requires C, 51·4; H, 5·2; N, 16·0%).

Reaction of the epoxide (3 g.) with magnesium bromide (15 g., from the elements) in ether (60 ml.) for 72 hr. at 5—10° gave 5-*acetoxy*-2-*bromo*-2-*methyl*cyclo*hexanol* (?) (2·8 g.), b. p. 106—114°/0·7 mm., n_D^{26} 1·4950—1·5028, ε <100 at λ 2200—4000 Å (Found: C, 44·2; H, 6·2; Br, 31·3. $C_9H_{15}O_3Br$ requires C, 43·0; H, 6·0; Br, 31·8%). From a lower-boiling fraction there was obtained 6-methyl*cyclo*hex-2-enone 2 : 4-dinitrophenylhydrazone, orange prisms [from benzene–light petroleum (b. p. 40—60°)], m. p. 162—163° (form *B*) (Found: C, 54·5; H, 5·2; N, 19·6. Calc. for $C_{13}H_{14}O_4N_4$: C, 53·8: H, 4·9; N, 19·3%).

2-*Acetoxy*-5-*methyl*cyclo*hexanone* 2 : 4-*Dinitrophenylhydrazone*.—Prepared from the ketone [27]

[27] Treibs and Bast, *Annalen*, 1949, **561**, 165.

this *derivative* crystallised from methanol–ethyl acetate in orange prisms, m. p. 168—170° (Found: C, 51·7; H, 5·5; N, 16·4. $C_{15}H_{18}O_6N_4$ requires C, 51·4; H, 5·2; N, 16·0%).

6-*Methyl*cyclo*hex*-3-*enone*.—*o*-Methoxytoluene (122 g., 1 mol.) in ether (500 ml.) was added in one lot to a stirred solution of lithium (30 g., 4·29 equiv.) in liquid ammonia (1·7 l.). After 15 min., dry ethanol (230 g., 5 mol.) was added dropwise during 30 min. After a further 5 min., when the intense blue colour of the solution had faded, the ammonia was allowed to evaporate, and the residue was stirred with 2N-sulphuric acid (800 ml.) at *ca.* 5° for 1 hr. The mixture was extracted with ether and the ether solution was separated, washed with dilute potassium hydroxide and water, dried (Na_2SO_4), and distilled, giving 6-*methyl*cyclo*hex*-3-*enone* (86 g., 78%), b. p. 59—60°/15 mm., n_D^{23} 1·4648, $\lambda_{max.}$ (in EtOH) 2730 Å (ε 70), $\nu_{max.}$ (liquid film) 1704 (C=O), 1653 (C=C) cm.$^{-1}$ (Found: C, 76·3; H, 9·4. $C_7H_{10}O$ requires C, 76·3; H, 9·15%). The 2 : 4-dinitrophenylhydrazone, prepared in ethanol–phosphoric acid, crystallised from aqueous ethanol in light orange prisms, m. p. 139°, $\lambda_{max.}$ (in EtOH) 3650 Å (ε 22,000) (lit.,[7] m. p. 135—137°).

Reaction of 6-*Methyl*cyclo*hex*-3-*enone with* 30% *Sulphuric Acid*.—When the crude ketone (40 g.) was boiled under reflux with 30% sulphuric acid (cf. ref. 7) for 30 min. it gave mainly a viscous, pale yellow *dimer* (27 g.), b. p. 120° (bath)/10^{-4} mm., n_D^{23} 1·5205, $\nu_{max.}$ (in CCl_4) 1718 (C=O) cm.$^{-1}$ (Found: C, 77·0; H, 9·2%; *M* in camphor, 235. $C_{14}H_{20}O_2$ requires C, 76·3; H, 9·15%; *M*, 220). A lower-boiling fraction, b. p. 67—70°/15 mm., n_D^{24} 1·4825, gave a 2 : 4-dinitrophenylhydrazone, crimson plates (from chloroform–methanol), m. p. 194—195°, $\lambda_{max.}$ (in $CHCl_3$) 3800 Å (ε 26,000), probably the derivative of 2-methyl*cyclo*hex-2-enone (see below); the latter ketone is known [28] to be present in small amount in the acid-rearrangement products from crude 6-methyl*cyclo*hex-3-enone.

6-*Methyl*cyclo*hex*-2-*enone*.—Crude 6-methyl*cyclo*hex-3-enone (85 g.), prepared as above, was heated under reflux with 2N-sulphuric acid (200 ml.) and methanol (10 ml.) for 3 hr. The product was isolated with ether, and the ether solution was washed, dried (Na_2SO_4), and distilled, giving crude ketone, b. p. 29—30°/0·2 mm. The combined product (176 g.) from two such runs was separated by fractionating through a 6″ Stedman column into 2-methyl*cyclo*hexanone (8 g.), b. p. 49—50°/15 mm., and 6-methyl*cyclo*hex-2-enone (103 g., 47%), b. p. 50—51°/15 mm., n_D^{20} 1·4834, $\lambda_{max.}$ (in EtOH) 2270 Å (ε 12,000), $\nu_{max.}$ (liquid film) 1680 (C=O), 1626 (C=C) cm.$^{-1}$ (Found: C, 76·5; H, 9·2. Calc. for $C_7H_{10}O$: C, 76·3; H, 9·15%) (lit.,[7] b. p. 164—167°, $\lambda_{max.}$ 2263 Å, ε 4490).

With 2 : 4-dinitrophenylhydrazine in ethanol–phosphoric acid, the ketone gave two derivatives which were separated by crystallisation. One was the 2 : 4-dinitrophenylhydrazone (form *B*) of 6-methyl*cyclo*hex-2-enone, which crystallised from ethyl acetate–methanol in light orange prisms, m. p. 155—156°, $\lambda_{max.}$ (in $CHCl_3$) 3790 Å (ε 24,000) (Found: C, 54·5; H, 5·2; N, 19·6. Calc. for $C_{13}H_{14}O_4N_4$: C, 53·8; H, 4·9; N, 19·3%) (lit.,[7,19,26] m. p. 156—157°, 161—162°, 162—164°). The other derivative, 5-(2 : 4-dinitrophenylhydrazino)-2-methyl*cyclo*hexanone 2 : 4-dinitrophenylhydrazone, crystallised from chloroform–dimethylformamide in orange plates, m. p. 187—188° (decomp.), $\lambda_{max.}$ (in $CHCl_3$) 3450 Å (ε 24,000) (Found: C, 46·3; H, 4·2; N, 22·9. Calc. for $C_{19}H_{20}O_8N_8$: C, 46·7; H, 4·1; N, 22·9%) (lit.,[7] m. p. 176—177°).

5-*Benzyloxy*-2-*methyl*cyclo*hexanone*.—A mixture of 6-methyl*cyclo*hex-2-enone (4·8 g.), benzyl alcohol (6·3 g.), boron trifluoride–ether complex (0·2 ml.), and yellow mercuric oxide (20 mg.) was kept at 100° for 3 hr. and then at room temperature for 35 days. Potassium carbonate (0·5 g.) was added and the mixture was distilled, giving unchanged ketone, benzyl alcohol, and a fraction (2·3 g.), b. p. 120°/0·2 mm., n_D^{23} 1·5367, which was treated with 2 : 4-dinitrophenylhydrazine in ethanol–phosphoric acid. The mixture of derivatives formed was separated by chromatography and gave (i) 6-methyl*cyclo*hex-2-enone 2 : 4-dinitrophenylhydrazone (?), m. p. 163° (Found: C, 53·0; H, 5·0; N, 19·8. Calc. for $C_{13}H_{14}O_4N_4$: C, 53·8; H, 4·9; N, 19·3%) (a mixture with the authentic specimen, m. p. 156—157°, described above, had m. p. 154—155°); and (ii) 5-*benzyloxy*-2-*methyl*cyclo*hexanone* 2 : 4-*dinitrophenylhydrazone*, orange plates (from ethyl acetate–pentane), m. p. 159—163°, $\lambda_{max.}$ (in $CHCl_3$) 3670 Å (ε 24,000) (Found: C, 59·9; H, 5·7; N, 14·1. $C_{20}H_{22}O_5N_4$ requires C, 60·3; H, 5·6; N, 14·1%).

Reduction of o-*Toluidine*.—(i) A solution of *o*-toluidine (10·5 g.) in dry ether (50 ml.) was added to a stirred solution of lithium (3·0 g.) in liquid ammonia (200 ml.). After 15 min., ethanol (30 ml.) was gradually added (20 min.), and stirring was maintained until the solution became colourless (13 min.). The ammonia was then allowed to evaporate, and the residue was decomposed with ice-water and extracted with ether. The ether solution was hydrogenated

[28] Birch and Hextall, *Austral. J. Chem.*, 1955, **8**, 96.

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over Raney nickel W7 (*ca.* 1 ml.) until absorption ceased (1790 ml.); distillation of the product gave mainly 2-methyl*cyclo*hexylamine (6·75 g.), b. p. 70—78°/51 mm., n_D^{22} 1·4611 (Found: C, 74·0; H, 13·1; N, 12·0. Calc. for $C_7H_{15}N$: C, 74·3; H, 13·35; N, 12·4%).

(ii) In a similar experiment, acetic acid (5 c.c.) was added to the ether extract; an oil separated. Raney nickel W7 (*ca.* 1 ml.) was added but no gas was absorbed when the mixture was shaken in hydrogen. More catalyst (1 ml.) was added, followed by sufficient ethanol (100 ml.) to render the sludge granular; hydrogen was then absorbed, and ceased after 16 hr. (950 ml.). Removal of solvent from the filtered solution gave an oil, which was heated to 90° in 20 min. with 2N-hydrochloric acid (100 ml.). Extraction of the cooled solution with ether gave 2-methyl*cyclo*hexanone (2·5 g.), b. p. 64°/19 mm., n_D^{22} 1·4483 (lit.,[29] b. p. 165°, n_D^{20} 1·4483), which showed light absorption in ethanol ($\lambda_{max.}$ 2270 Å, ε *ca.* 400) indicating the presence of a very small proportion of 6-methyl*cyclo*hex-2-enone.

Reduction of Anisidines.—(i) *o*-Anisidine (12·3 g.) was reduced with lithium in liquid ammonia in the same way as *o*-toluidine. After evaporation of the ammonia the residue was dissolved in ice-water and extracted with ether. Evaporation of these extracts gave an oil, which was treated for a few minutes on the steam-bath with 2N-hydrochloric acid and worked up with ether, to give *cyclo*hex-2-enone (3·5 g.), b. p. 77—80°/12 mm., n_D^{23} 1·4817, $\lambda_{max.}$ (in EtOH) 2250 Å (ε 4800) [semicarbazone, m. p. 164—166°, $\lambda_{max.}$ (in EtOH) 2300, 2700 Å (ε 8000, 7000)] (lit.,[30] b. p. 169—171°, n_D^{18} 1·4842; semicarbazone, m. p. 171—172°).

(ii) *p*-Anisidine (12·3 g.) on similar reduction gave *cyclo*hexane-1 : 4-dione (1·3 g.), m. p. 78° (lit.,[30] m. p. 78°).

2 : 4-*Dihydroxybenzaldehyde.*—Prepared by Bisagni, Buu-Hoï, and Royer's method,[31] except that the product was not distilled but was directly recrystallised from water, it was obtained in better yield (55% on a 2 mole scale), and had m. p. 135—136° (lit.,[31] m. p. 135°), $\lambda_{max.}$ (in Et_2O) 2320, 2800, and 3100 Å (ε 8600, 13,800, and 6600), $\nu_{max.}$ (in $CHCl_3$) 3509 (O–H), 1658, and 1634 (chelated –CHO) cm.$^{-1}$.

2 : 4-*Dihydroxybenzaldehyde Azine.*—A mixture of the aldehyde (2 g.) with a large excess of 100% hydrazine hydrate (5 g.) was heated at 100° for 5 min., then cooled and acidified with dilute acetic acid. The yellow precipitate on recrystallisation from hot water or aqueous dioxan gave yellow needles of the *azine* (1·7 g.), which sublimed at *ca.* 270° and did not melt at 315°; it had $\lambda_{max.}$ (in EtOH) 2220, 2500, 3100, and 3650 Å (ε 16,300, 13,600, 12,800, and 48,000) (Found: C, 61·8; H, 4·8; N, 10·7. $C_{14}H_{12}O_4N_2$ requires C, 61·8; H, 4·4; N, 10·3%).

Treatment of the azine (5 g.) with potassium hydroxide (5 g.) and sodium (0·5 g.) in ethylene glycol (20 ml.) for 2·5 hr. at 170° under nitrogen gave only a brown resin. A similar result was obtained by reaction of the azine with a fused 1 : 1 mixture of sodium hydroxide and potassium hydroxide at 150—300°.

4-*Methyl*cyclo*hexane*-1 : 3-*diol.*—A solution of 2 : 4-dihydroxybenzaldehyde (13·8 g.) and sodium hydroxide (0·2 g.) in methanol (100 ml.) was hydrogenated over freshly prepared Raney nickel W7 (*ca.* 5 g.) at 100°/140 atm. until absorption ceased (4 hr.). The filtered solution was then neutralised with hydrochloric acid and distilled to give 4-*methyl*cyclo*hexane*-1 : 3-*diol* (12 g., 92%), b. p. 150° (bath)/10^{-3} mm., $\nu_{max.}$ (in CCl_4) 3630 (free O–H), 3542 (bonded O–H) cm.$^{-1}$ (Found: C, 63·9; H, 10·7. $C_7H_{14}O_2$ requires C, 64·6; H, 10·8%). A small amount of solid was collected from the last fraction; on recrystallisation from acetone–light petroleum (b. p. 40—60°) it formed plates, m. p. 107—108°, $\nu_{max.}$ (paraffin mull) 3268 (O–H) (Found: C, 63·9; H, 10·9%). Purity of the aldehyde and high activity of the catalyst are essential for the success of this reduction.

With ether as solvent in place of methanol, the product was *trans*-2-methyl*cyclo*hexanol (71%), b. p. 33—35°/0·02 mm., n_D^{22} 1·4607—1·4619 (Found: C, 73·7; H, 12·5. Calc. for $C_7H_{14}O$: C, 73·6; H, 12·4%), identified as the 3 : 5-dinitrobenzoate, m. p. 112—115° (lit.,[32] m. p. 117°).

Monobenzoylation of 4-*Methyl*cyclo*hexane*-1 : 3-*diol.*—Benzoyl chloride (40 g.) in chloroform (100 ml.) was gradually added to the diol (37 g.) in pyridine (40 g.), vigorously stirred at −10°. The mixture was set aside overnight, then heated at 100° for 1 hr., cooled to −10°, diluted with water, and acidified with hydrochloric acid. The chloroform layer was washed with dilute

[29] Skita, *Ber.*, 1923, **56**, 1014.
[30] Bartlett and Woods, *J. Amer. Chem. Soc.*, 1940, **62**, 2933.
[31] Bisagni, Buu-Hoi, and Royer, *J.*, 1955, 3693.
[32] Jackman, Macbeth, and Mills, *J.*, 1949, 1717.

hydrochloric acid, aqueous sodium carbonate and water, then dried ($MgSO_4$) and evaporated to give the *monobenzoate* (mainly 5-benzoyloxy-2-methyl*cyclo*hexanol) as a viscous oil (52 g.). A portion was distilled at 150—180° (bath)/10^{-5} mm., and showed $\nu_{max.}$ (in CCl_4) 3610 and 3497 (O–H), 1718 (C=O), 1274 and 1112 (benzoate) cm.$^{-1}$ (Found: C, 71·6; H, 7·6. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%).

Oxidation. This monobenzoate (23·4 g.) in acetic acid (30 g.) and water (10 g.) was added dropwise to a stirred solution of chromium trioxide (14 g.) in acetic acid (60 g.) and water (20 g.) at 0°. Stirring was maintained for 3 hr. at 0° and 24 hr. at room temperature, and most of the acetic acid was then neutralised with aqueous sodium hydroxide. Continuous extraction with ether, and distillation of the washed (aq. Na_2CO_3) extract, gave an oil (4·5 g.), b. p. 50—90°/10^{-4} mm., n_D^{24} 1·4936—1·5002, and a sublimate of benzoic acid, m. p. and mixed m. p. 122°. Treatment of the oil with 2 : 4-dinitrophenylhydrazine in phosphoric acid gave 5-(2 : 4-dinitrophenylhydrazino)-2-methyl*cyclo*hexanone 2 : 4-dinitrophenylhydrazone, m. p. 187—188°, mixed m. p. 184—185°.

Monobenzoylation of 2 : 4-*Dihydroxybenzaldehyde.*—(i) Benzoyl chloride (4·6 ml.) was added dropwise, with shaking, to the aldehyde (5·6 g.) in 0·24N-potassium hydroxide (185 ml.), the precipitated lumps of derivative being removed at intervals. A solution of the crude product in benzene–light petroleum (b. p. 60—80°) slowly deposited 2-*benzoyloxy*-4-*hydroxybenzaldehyde* (2·1 g.) which on recrystallisation from benzene formed plates, m. p. 136—137° (Found: C, 69·7; H, 4·3. $C_{14}H_{10}O_4$ requires C, 69·4; H, 4·2%). The 4-benzoyloxy-compound, m. p. 102—103° (see below), was isolated from the mother-liquors.

(ii) A similar procedure was carried out on the aldehyde (45 g.), and the crude product was crystallised twice from ethanol to give 4-benzoyloxy-2-hydroxybenzaldehyde (27 g.), m. p. 101—102°. Leon and Robinson,[24] who proved its structure, give m. p. 103°.

Hydrogenation of 4-*Benzoyloxy*-2-*hydroxybenzaldehyde.*—The aldehyde (4·8 g.) in dry ether (100 ml.) was hydrogenated over Raney nickel W7 for 14 hr. at 100°/100 atm. Distillation of the product gave a series of fractions the last of which (0·5 g.), b. p. 164—192° (bath)/10^{-4} mm., solidified. Recrystallisation from benzene–light petroleum gave prisms of (?) 3-hydroxy-4-methyl*cyclo*hexyl benzoate, m. p. 100—101°, $\nu_{max.}$ (paraffin mull) 3304 (O–H), 1714 (C=O in aromatic ester), 1606 and 1509 (benzenoid) cm.$^{-1}$ (Found: C, 71·7; H, 8·0. Calc. for $C_{14}H_{18}O_3$: C, 71·75; H, 7·7%).

4-*Methyl*-3-*nitrophenol.*—Prepared by Copisarow's method,[33] this had m. p. 78—79° (lit.,[33] m. p. 76—77°). The *acetate*, m. p. 70—71° (Found: C, 55·3; H, 4·75; N, 7·3. $C_9H_9O_4N$ requires C, 55·4; H, 4·65; N, 7·2%), and the *benzoate*, m. p. 94—95° (Found: C, 65·1; H, 4·3; N, 5·65. $C_{14}H_{11}O_4N$ requires C, 65·4; H, 4·3; N, 5·4%), both formed pale yellow needles from ethanol.

3-*Amino*-4-*methylphenyl Acetate.*—4-Methyl-3-nitrophenyl acetate (2·0 g.) was hydrogenated in methanol (20 ml.) over Raney nickel W7 (*ca* 1 ml.) and magnesium sulphate (0·1 g.) at 25°/40 atm. for 24 hr. to give the *amine* (1·4 g.), m. p. 72—73° [from benzene–light petroleum (b. p. 60—80°)] (Found: C, 65·9; H, 6·6; N, 8·6. $C_9H_{11}O_2N$ requires C, 65·5; H, 6·7; N, 8·5%).

3-*Amino*-4-*methylphenyl Benzoate.*—4-Methyl-3-nitrophenyl benzoate (2·6 g.), water (20 ml.), and acetic acid (0·3 ml.) were boiled under reflux during the gradual addition (1·5 hr.) of iron filings (2 g.). Boiling was continued for another hour, and the mixture was then filtered and evaporated. Recrystallisation of the residue from ethanol gave colourless needles of the *amine* (1·3 g.), m. p. 113—114° (Found C, 73·6; H, 5·8; N, 6·5. $C_{14}H_{13}O_2N$ requires C, 74·0; H, 5·8; N, 6·2%). The same product was obtained, in poorer yield, by hydrogenation, as described above for the acetate.

3-*Hydroxy*-4-*methylphenyl Benzoate.*—The precipitate formed by the addition of 3-amino-4-methylphenyl benzoate (5·1 g.) to a solution of stannic chloride (8 ml.) in concentrated hydrochloric acid (20 ml.) was collected, suspended in concentrated hydrochloric acid (20 ml.), and cooled.[34] A solution of sodium nitrite (1·4 g.) in water (4·5 ml.) was added slowly (20 min.) at *ca.* 5° with stirring, which was maintained for a further hour. The precipitate was collected and added during 10 min. to boiling water (150 ml.). Extraction of the cooled solution with ether gave a solid which was dissolved in ethanol, filtered from some insoluble material, and evaporated to an oil, which after distillation at 230° (bath)/10^{-4} mm. solidified (1·5 g.).

[33] Copisarow, *J.*, 1929, 251.
[34] Cf. Woodward and Doering, *J. Amer. Chem. Soc.*, 1945, **67**, 860.

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Recrystallisation from aqueous ethanol gave *3-hydroxy-4-methylphenyl benzoate*, colourless prisms, m. p. 107—109° (Found: C, 73·4; H, 5·6. $C_{14}H_{12}O_3$ requires C, 73·7; H, 5·3%).

The residual aqueous solution was made alkaline and extracted with ether; 3-amino-4-methylphenyl benzoate (1·1 g.), m. p. 110—113°, was recovered.

Grateful acknowledgment is made to the Distillers' Company for a Studentship (to A. A. W., 1954—56), and to the Salters' Company for a Scholarship (A. A. W., 1956—57). One of us (M. U. S. S.) thanks the Council of the University of Ceylon for one year's sabbatical leave.

DEPARTMENT OF CHEMISTRY,
IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
SOUTH KENSINGTON, LONDON, S.W.7. [*Received, May 19th*, 1958.]

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678. *Studies in the Vitamin D Field. Part IV.*[1] *The Synthesis of Some Ring A Derivatives.*

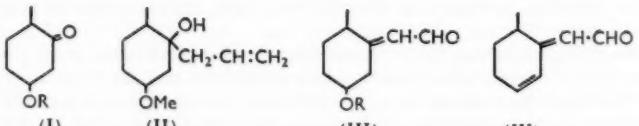
By (the late) E. A. BRAUDE, M. U. S. SULTANBAWA, and A. A. WEBB.

Syntheses of 5-methoxy-2-methyl*cyclo*hexylideneacetaldehyde (III; R = Me) from 5-methoxy-2-methyl*cyclo*hexanone, and of 3-ethynyl-4-methyl*cyclo*hex-2-enol (VI; R = H) from 6-methyl*cyclo*hex-2-enone, are described; these compounds are of potential use for the synthesis of 9 : 10-*seco*-steroids and related substances. Some pilot experiments involving the synthesis of 6-methyl-1-phenyl*cyclo*hex-2-enol and some transformation products are recorded.

The CD-ketone derived from ergocalciferol has been converted into 4-chloro-6 : 7 : 8 : 9-tetrahydro-8-methyl-1-(1 : 4 : 5-trimethylhex-2-enyl)indane (XII; R = Cl).

IN Part I,[2] some simple analogues of tachysterol were synthesised by condensation of *cyclo*hexenyl-lithium with *cyclo*hexylidene- and 2'-methyl*cyclo*hexylidene-acetaldehyde. For a synthesis of tachysterol itself along these lines an aldehyde of type (III) is required. Efforts to achieve simpler syntheses of the necessary ketone (I) having proved impracticable,[1] the methoxy-compound (I; R = Me) was prepared by the recorded method [3] from *p*-cresol. Details of the later stages of this preparation are given on p. 3338 since the conditions for satisfactory yields are important.

Reaction of 5-methoxy-2-methyl*cyclo*hexanone (I; R = Me) with allylmagnesium chloride gave 1-allyl-2-methyl-5-methoxy*cyclo*hexanol (II) which on ozonolysis, followed by distillation of the product over potassium hydrogen sulphate, furnished an unsaturated



(I) (II) (III) (IV)

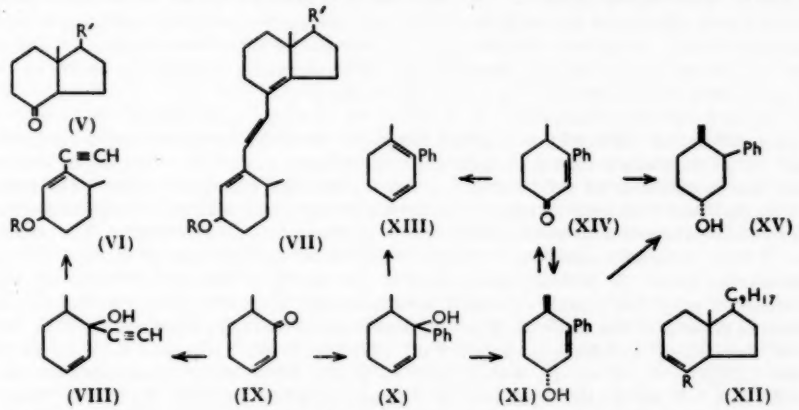
aldehyde; from its light absorption ($\lambda_{max.}$ 2370 Å, ε 9500 in EtOH) this consisted largely of the required 5-methoxy-2-methyl*cyclo*hexylideneacetaldehyde (III; R = Me). As was observed [2] with the analogous compound lacking the methoxy-group, the free aldehyde was unstable and gave unsatisfactory analytical results, but it readily yielded a pure semicarbazone and a pure 2 : 4-dinitrophenylhydrazone, the spectral characteristics of which agreed with the αβ-unsaturated structure. Prolonged treatment of the aldehyde (III; R = Me) with potassium hydrogen sulphate gave a product which showed an additional absorption maximum at 2800 Å, indicating that elimination had occurred to

[1] Part III, preceding paper.
[2] Braude and Wheeler, *J.*, 1955, 320.
[3] U.S.P. 2,511,815.

some extent to give the conjugated dienal (IV); the 2 : 4-dinitrophenylhydrazone prepared from such a product showed light absorption and analytical figures compatible with a parent compound having this structure.

An acetylenic compound (VI) is clearly of potential synthetical use in this field; for example, condensation with the CD-ketone (V), followed by partial reduction and dehydration, could give the μ-tachysterol [4] derivative (VII). A pilot investigation was carried out on the reaction of 6-methyl*cyclo*hex-2-enone (IX) with phenylmagnesium bromide, which gave 6-methyl-1-phenyl*cyclo*hex-2-enol (X) in good yield. This rearranged in acidified aqueous acetone to the conjugated alcohol (XI); a small amount of a solid hydrocarbon, probably 1-methyl-2-phenyl*cyclo*hexa-1 : 3-diene (XIII), was also formed. Oxidation of the alcohol (XI) with chromium trioxide in pyridine gave 4-methyl-3-phenyl*cyclo*hex-2-enone (XIV), and when this was reduced with lithium aluminium hydride the original alcohol (XI), together with a large amount of hydrocarbon, was formed. Since reduction of unhindered ketones with lithium aluminium hydride normally [5] gives the equatorial epimer the alcohol can be allocated the *trans*-configuration shown (formulæ refer to optically inactive materials), in which the methyl and the hydroxyl group are both in quasi-equatorial [5] positions. Catalytic hydrogenation of this alcohol, and also reduction of the ketone (XIV) with sodium in propan-2-ol, gave the same saturated alcohol, 4-methyl-3-phenyl*cyclo*hexanol (XV).

3-Ethynyl-4-methyl*cyclo*hex-2-enol (VI; R = H) was then prepared by a similar sequence of reactions. Conjugated unsaturated ketones do not readily react with metal acetylides in liquid ammonia (*iso*phorone is notoriously inactive [6]), and 6-methyl*cyclo*hex-2-enone (IX) with lithium acetylide gave only an impure alcohol containing much unchanged ketone. Pure 1-ethynyl-6-methyl*cyclo*hex-2-enol (VIII) was obtained, however, by reaction of the ketone with acetylene monomagnesium bromide in tetrahydrofuran



under the conditions recently described [7] for the preparation of this reagent.* Rearrangement in acidified aqueous acetone proceeded smoothly to give the desired product (VI; R = H), which readily gave the tetrahydropyranyl ether (VI; R = C_5H_9O).

A possible partial synthesis of the tachysterol system would involve condensation of an aldehyde (III) with the alkenyl-lithium (XII; R = Li) according to the general method suggested in Part I,[2] and an investigation was therefore made of the conversion of the

* We are much indebted to Professor E. R. H. Jones, F.R.S., for informing us about this method before its publication.

[4] Inhoffen, Brückner, Irmscher, and Quinkert, *Chem. Ber.*, 1955, **88**, 1424.
[5] Barton and Cookson, *Quart. Rev.*, 1956, **10**, 44.
[6] Oroshnik and Mebane, *J. Amer. Chem. Soc.*, 1949, **71**, 2062.
[7] Jones, Skatteböl, and Whiting, *J.*, 1956, 4765.

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C_{19} ketone (V; R′ = C_9H_{17}), derived [8,9] from ergocalciferol, into the chloro-compound (XII; R = Cl) by reaction with phosphorus pentachloride. The product was analytically pure, but could, of course, be a mixture of (XII; R = Cl) and the isomer with the double bond in the bridgehead position. The far-ultraviolet absorption spectrum was kindly measured with a double-beam photoelectric recording vacuum spectrophotometer [10] by Dr. D. W. Turner, who reported that " it shows (in hexane) only one broad band ($\lambda_{max.}$ 1900 Å, ε 17,500), which is consistent with a summation of the absorptions due to the olefinic side chain and the 4 : 5-double bond, as in (XII; R = Cl) (cf. ergost-22-enyl acetate, $\lambda_{max.}$ 1850 Å, ε 11,600; and 1-chloro*cyclo*hexene, $\lambda_{max.}$ 1950 Å, ε 6,400). The 4 : 9-isomer would probably show a separate maximum above 2100 Å [cf. ergost-8(14)-enol, $\lambda_{max.}$ 2080 Å, ε 11,200]." Thus it seems unlikely that the product contained any significant proportion of the 4 : 9-isomer, and we accordingly regard it as the required 4-chloro-6 : 7 : 8 : 9-tetrahydro-8-methyl-1-(1 : 4 : 5-trimethylhex-2-enyl)indane (XII; R = Cl).

Experimental

5-Methoxy-2-methylphenol.—Sodium nitrite (34·5 g.) in water (135 ml.) was added at 0—5° to a mixture of 5-methoxy-2-methylaniline [11] (69 g.), sulphuric acid (55 ml.), and water (1 l.). This solution was then slowly added (20 min.) to a boiling mixture of benzene (1030 ml.), water (710 ml.), and sulphuric acid (355 ml.); boiling was continued for a further 15 min. and the mixture was then cooled. The benzene layer was removed, the aqueous portion was extracted with benzene, and the combined benzene solutions were dried (Na_2SO_4) and evaporated to a semi-solid residue (69 g.). The combined products (251 g.) from four such experiments were steam-distilled, and the 5-methoxy-2-methylphenol (176 g., 63%), m. p. 42—43°, isolated by extraction of the distillate with benzene (lit.,[12] m. p. 47°).

*5-Methoxy-2-methyl*cyclo*hexanol.*—The above phenol (137 g.) in methanol (500 ml.) was hydrogenated over Raney nickel W7 at 120—130°/130 atm. for 60 hr. The crude product was washed with alkali, and the residual neutral material distilled to give 5-methoxy-2-methyl-*cyclo*hexanol (111 g.), b. p. 84—110°/14 mm., n_D^{25} 1·4608—1·4656. Redistillation of a portion gave a main fraction, b. p. 86—93°/14 mm., n_D^{23} 1·4609 (Found: C, 67·2; H, 11·4. Calc. for $C_8H_{16}O_2$: C, 66·6; H, 11·2%) (lit.,[3] b. p. 74—93°/8 mm.).

*5-Methoxy-2-methyl*cyclo*hexanone.*—A solution of chromic acid (35 g.) in acetic acid (53·5 ml.) and water (53·5 ml.) was added dropwise (50 min.) to 5-methoxy-2-methyl*cyclo*hexanol (61 g.) in benzene (650 ml.), with vigorous stirring, at *ca.* 50°. Stirring at this temperature was maintained for a further 3 hr., and the mixture was then cooled. The benzene layer was combined with benzene extracts of the aqueous portion, washed with aqueous sodium hydrogen carbonate and with water, dried, and evaporated to an oil (57·5 g.). The combined product (129 g.) from such oxidation of 134 g. of the alcohol on fractional distillation through a Fenske column gave: (i) 2-methyl*cyclo*hexanone (17 g.), b. p. 55—56°/16 mm., n_D^{22} 1·4490 (semicarbazone, m. p. 191°) (lit.,[13] n_D^{20} 1·4483, semicarbazone, m. p. 191°), derived from 2-methyl-*cyclo*hexanol present in the crude alcohol; (ii) 5-methoxy-2-methyl*cyclo*hexanone (81 g., 60%), b. p. 94°/16 mm., n_D^{23} 1·4559, $\nu_{max.}$ (liquid film) 1707 (C=O) cm.$^{-1}$ (Found: C, 67·5; H, 10·3. Calc. for $C_8H_{14}O_2$: C, 67·6; H, 9·9%) (lit.,[3] b. p. 83—87°/8 mm.) [semicarbazone, m. p. 167—168° (lit.,[14,15] m. p. 167°, 158—159°) (Found: C, 54·4; H, 8·6; N, 21·15. Calc. for $C_9H_{17}O_2N_3$: C, 54·3; H, 8·6; N, 21·1%)].

*1-Allyl-5-methoxy-2-methyl*cyclo*hexanol.*—A mixture of 5-methoxy-2-methyl*cyclo*hexanone (21·3 g.), allyl chloride (14·4 g.), benzene (30 ml.), and dry ether (75 ml.) was added dropwise (3·5 hr.) to a stirred mixture of magnesium (4·0 g.), ether (40 ml.), and iodine (trace), the bath-temperature being maintained at 35—40° during the first 2·5 hr. and gradually raised to 50° during the final hour. The cooled mixture was then treated at 0° with ammonium chloride

[8] Windaus and Grundmann, *Annalen*, 1936, **524**, 295.
[9] Dimroth and Jonsson, *Ber.*, 1941, **74**, 520.
[10] D. W. Turner, *J.*, 1957, 4555.
[11] Beaven, Bird, Hall, Lesslie, and E. E. Turner, *J.*, 1954, 131.
[12] Limpach, *Ber.*, 1891, **24**, 4139.
[13] Skita, *Ber.*, 1923, **56**, 1014.
[14] Inhoffen, Weissermel, and Quinkert, *Chem. Ber.*, 1955, **88**, 1313.
[15] Corsano and Capitò, *Gazzetta*, 1955, **85**, 1590.

(60 g.) in water (100 ml.), and filtered. The aqueous portion of the filtrate was extracted with ether, and the combined organic layers were dried and distilled to give *1-allyl-5-methoxy-2-methylcyclohexanol* (14 g., 50%), b. p. 91—94°/0·9 mm., n_D^{24} 1·4710, $\nu_{max.}$ (liquid film) 3454 (O–H), 1635 (C=O) cm.$^{-1}$ (Found: C, 71·5; H, 11·0. $C_{11}H_{20}O_2$ requires C, 71·7; H, 10·9%).

5-Methoxy-2-methylcyclohexylideneacetaldehyde.—The preceding compound (10·0 g.) in acetic acid (50 ml.) was ozonised at 0° for 14 hr. Zinc dust (10 g.) was then added, and the mixture was heated on the steam-bath for 20 min., then poured on ice and extracted with ether to give a product (2·7 g.), b. p. 80—100°/0·3 mm., n_D^{24} 1·4779, $\lambda_{max.}$ (in C_6H_{14}) 2370 Å (ε 8400). It was redistilled over fused potassium hydrogen sulphate (0·3 g.) to give *5-methoxy-2-methylcyclohexylideneacetaldehyde*, b. p. 91—92°/0·2 mm., n_D^{22} 1·4910, $\lambda_{max.}$ (in C_6H_{14}) 2370 Å (ε 9400), $\nu_{max.}$ (liquid film) 3430 (weak; trace of hydroxy-compound), 2720 (C–H in CHO), 1715 and 1667 (C=O), 1627 (C=O) cm.$^{-1}$ (Found: C, 67·1, 68·3; H, 9·6, 9·6. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%). It gave a *semicarbazone* (from aqueous ethanol), m. p. 172—174°, $\lambda_{max.}$ (in EtOH) 2740 (ε 37,400) (Found: C, 59·05; H, 8·3; N, 19·0. $C_{11}H_{19}O_2N_3$ requires C, 58·6; H, 8·5; N, 18·65%), and a *2 : 4-dinitrophenylhydrazone*, orange rosettes (from benzene), m. p. 183°, $\lambda_{max.}$ (in $CHCl_3$) 3850 Å (ε 31,000) (Found: C, 55·7; H, 5·9; N, 15·6. $C_{16}H_{20}O_5N_4$ requires C, 55·15; H, 5·8; N, 16·1%).

In another experiment, the product was distilled twice over potassium hydrogen sulphate, and then had b. p. 87°/0·2 mm., n_D^{24} 1·4944, $\lambda_{max.}$ (in EtOH) 2400 and 2800 (ε 4200 and 760) (Found: C, 71·2; H, 9·8%). With 2 : 4-dinitrophenylhydrazine in phosphoric acid it gave, after chromatography, *2-methylcyclohex-5-enylideneacetaldehyde 2 : 4-dinitrophenylhydrazone*, dark red prisms [from benzene–light petroleum (b. p. 60—80°)], m. p. 164—166°, $\lambda_{max.}$ (in $CHCl_3$) 3100 and 3960 Å (ε 12,000 and 35,700) (Found: C, 57·1; H, 5·4; N, 17·8. $C_{15}H_{16}O_4N_4$ requires C, 57·0; H, 5·1; N, 17·7%).

6-Methyl-1-phenylcyclohex-2-enol.—A solution of 6-methylcyclohex-2-enone [1] (22·0 g.) in ether (50 ml.) was slowly added (30 min.) at 0° to a Grignard reagent prepared from magnesium (6 g.), bromobenzene (33 g.), and ether (100 ml.). Stirring was continued for 2·5 hr. at room temperature, and the complex was then decomposed by the addition of excess of aqueous ammonium chloride. The ether layer, and ethereal extracts of the aqueous layer, were combined, dried ($Na_2SO_4 + K_2CO_3$), and distilled from a trace of potassium carbonate to give 6-methyl-1-phenylcyclohex-2-enol (28·3 g., 75%), b. p. 86—87°/10^{-3} mm., n_D^{23} 1·5529, $\lambda_{max.}$ (in EtOH) 2520 Å (ε 1900), $\nu_{max.}$ (liquid film) 3367 (O–H) cm.$^{-1}$ (Found: C, 83·4, 83·6; H, 8·7, 8·6. $C_{13}H_{16}O$ requires C, 82·9; H, 8·6%).

4-Methyl-3-phenylcyclohex-2-enol.—A mixture of 6-methyl-1-phenylcyclohex-2-enol (20·6 g.), acetone (600 ml.), water (400 ml.), and 2N-hydrochloric acid (5 ml.) was set aside for 24 hr., then neutralised with sodium hydrogen carbonate. The acetone was distilled off through a short column, and the residual aqueous solution was extracted with chloroform to give, on distillation: (i) a white solid (1 g.), probably *1-methyl-2-phenylcyclohexa-1 : 3-diene*, b. p. 120—130° (bath)/10^{-3} mm., which crystallised from aqueous methanol in plates, m. p. 69—70°, $\lambda_{max.}$ (in EtOH) 2480 Å (ε 17,700) (Found: C, 91·6, 91·3; H, 6·6, 6·55; O, nil. $C_{13}H_{14}$ requires C, 91·7; H, 8·3%); and (ii) *4-methyl-3-phenylcyclohex-2-enol* (17·4 g., 84%), b. p. 105—107°/10^{-3} mm., n_D^{23} 1·5672, $\lambda_{max.}$ 2410 Å (ε 12,800), $\nu_{max.}$ (liquid film) 3311 (O–H), 1642 (C=C) cm.$^{-1}$ (Found: C, 82·85; H, 8·8. $C_{13}H_{16}O$ requires C, 82·9; H, 8·6%). Like the unconjugated isomer, it gave an intense green colour with concentrated sulphuric acid. The *3 : 5-dinitrobenzoate* formed needles (from aqueous acetone), m. p. 128° (Found: C, 62·55; H, 5·0; N, 7·3. $C_{20}H_{18}O_6N_2$ requires C, 62·8; H, 4·75; N, 7·3%).

4-Methyl-3-phenylcyclohex-2-enone.—Chromium trioxide (15 g.) was added in small portions to stirred pyridine (200 ml.) below 20°. The mixture was then cooled to 0°, a solution of 4-methyl-3-phenylcyclohex-2-enol (11 g.) in pyridine (100 ml.) was gradually added, and the whole was kept at 5—10° for 3 days. The pyridine was then removed under reduced pressure at 20°, and the residue was treated with ether and water. Distillation of the dried ethereal solution afforded the *ketone* (10·3 g., 95%), b. p. 92—94°/0·01 mm., n_D^{23} 1·5893, $\lambda_{max.}$ (in EtOH) 2800 Å (ε 18,000), $\nu_{max.}$ (liquid film) 1672 (C=O) (Found: C, 83·9; H, 7·7. $C_{13}H_{14}O$ requires C, 83·8; H, 7·6%). The *2 : 4-dinitrophenylhydrazone* formed crimson needles (from ethyl acetate–methanol), m. p. 190°, $\lambda_{max.}$ (in $CHCl_3$) 4000 Å (ε 33,000) (Found: C, 62·3; H, 5·0; N, 15·9. $C_{19}H_{18}O_4N_4$ requires C, 62·3; H, 4·95; N, 15·3%).

Reduction of 4-Methyl-3-phenylcyclohex-2-enone.—(i) *With lithium aluminium hydride.* The ketone (2·5 g.) in ether (25 ml.) was added to a solution of lithium aluminium hydride (0·5 g.)

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in ether (75 ml.) and the mixture was stirred for 30 min. and then cooled to 0° and acidified with hydrochloric acid. Isolation with ether afforded a pale yellow viscous liquid (1·8 g.), b. p. 130—150° (bath)/10^{-4} mm., n_D^{22} 1·5818—1·5840, $\lambda_{max.}$ (in EtOH) 2280, 2340, and 3050 Å (ε 10,000, 10,000, and 10,000) (Found: C, 88·5; H, 8·65. Calc. for $C_{13}H_{16}O$: C, 82·9; H, 8·6. Calc. for $C_{13}H_{14}$: C, 91·7; H, 8·3%); it gave 4-methyl-3-phenyl*cyclo*hex-2-enyl 3 : 5-dinitrobenzoate, m. p. and mixed m. p. 126—127°.

(ii) *With sodium and propanol.* Sodium (15 g.) was gradually added (30 min.) to a boiling solution of 4-methyl-3-phenyl*cyclo*hex-2-enone (3·0 g.) in propanol (100 ml.). Boiling was continued for a further 25 min., and the remaining sodium was decomposed by the addition of methanol (50 ml.) and water (15 ml.). The solvents were then removed under reduced pressure and the residue was treated with ether and water. Distillation of the dried ethereal solution gave *4-methyl-3-phenyl*cyclo*hexanol* (2·9 g., 97%), b. p. 105—110°/10^{-2} mm., n_D^{23} 1·5421, $\lambda_{max.}$ (in EtOH) 2420 Å (ε 380), $\nu_{max.}$ (liquid film) 3333 (O–H) (Found: C, 81·5; H, 9·6. $C_{13}H_{18}O$ requires C, 82·1; H, 9·5%). It had an odour of limonene. The 3 : *5-dinitrobenzoate* formed needles [from acetone–light petroleum (b. p. 40—60°)], m. p. 133—135°, $\lambda_{max.}$ (in EtOH) 2320 (ε 24,000) (Found: C, 62·6; H, 5·6. $C_{20}H_{20}O_6N_2$ requires C, 62·5; H, 5·2%).

*Hydrogenation of 4-Methyl-3-phenyl*cyclo*hex-2-enol.*—The alcohol (1·5 g.) in methanol (25 ml.) absorbed 248 ml. (calc. 250 ml.) of hydrogen at 24°/752 mm. during 15 min. over 10% palladised charcoal (0·1 g.). Evaporation of the filtered solution gave 4-methyl-3-phenyl*cyclo*hexanol (1·4 g.), identified as the 3 : 5-dinitrobenzoate, m. p. and mixed m. p. 133—134°.

*1-Ethynyl-6-methyl*cyclo*hex-2-enol.*—A Grignard reagent was prepared from ethyl bromide (23 g.) and magnesium (5 g.) in boiling tetrahydrofuran (100 ml.), and added dropwise whilst still hot, during 25 min., to tetrahydrofuran (100 ml.) through which a rapid stream of acetylene was passed at room temperature. After 1 hr., the gas stream was reduced to a slow flow, and the solution was cooled to −10°. 6-Methyl*cyclo*hex-2-enone [1] (11·0 g.) in tetrahydrofuran (50 ml.) was added, and the mixture was stirred for 18 hr. at room temperature, the slow stream of acetylene being maintained. An excess of saturated aqueous ammonium chloride was then added at 0°, and the organic layer was removed and combined with ethereal extracts of the aqueous layer (on a larger scale it is preferable to distill off the tetrahydrofuran through a column, dilute the residue with water, and extract it with chloroform). Removal of solvent from the dried (Na_2SO_4 + K_2CO_3) extract, and distillation of the residue, gave *1-ethynyl-6-methyl*cyclo*hex-2-enol* (7·3 g., 54%), b. p. 44—45°/10^{-4} mm., n_D^{23} 1·4990, no strong absorption between 2000 and 4000 Å, $\nu_{max.}$ (in CCl_4) 3623 and 3472 (O–H), 3300 (≡C–H), 3030 (=C–H), 2924 (C–H), 2123 (C≡CH), 1656 (C=C) cm.$^{-1}$ (Found: C, 79·5; H, 9·0. $C_9H_{12}O$ requires C, 79·4; H, 8·9%).

An identical experiment, but with the ethylmagnesium bromide prepared in ether, gave a yield of only 39%.

*3-Ethynyl-4-methyl*cyclo*hex-2-enol.*—A mixture of 1-ethynyl-6-methyl*cyclo*hex-2-enol (44 g.), acetone (400 ml.), water (350 ml.), and 2N-hydrochloric acid (50 ml.) was set aside for 24 hr., then neutralised with sodium hydrogen carbonate, concentrated to remove acetone, and extracted with ether to give *3-ethynyl-4-methyl*cyclo*hex-2-enol* (40 g., 90%), b. p. 60—61°/10^{-3} mm., n_D^{24} 1·5109, $\lambda_{max.}$ (in EtOH) 2260 Å (ε 9,000), $\nu_{max.}$ (in CCl_4) 3610 (O–H), 3279 (≡C–H), 3021 (=C–H), 2933 and 2865 (C–H), 2105 (C≡CH), 1623 (C=C) cm.$^{-1}$ (Found: C, 79·6; H, 9·0. $C_9H_{12}O$ requires C, 79·4; H, 8·9%). The compound was unstable in air, and became yellow in a few hours. The 3 : *5-dinitrobenzoate* formed colourless prisms (from acetone–pentane), m. p. 94—95°, $\lambda_{max.}$ (in EtOH) 2270 Å (ε 43,000) (Found: C, 57·65; H, 4·5; N, 9·2. $C_{16}H_{14}O_6N_2$ requires C, 58·2; H, 4·3; N, 8·5%).

*3-Ethynyl-4-methyl*cyclo*hex-2-enyl Tetrahydropyran-2-yl Ether.*—A mixture of 2 : 3-dihydro-4*H*-pyran (50 ml.), 3-ethynyl-4-methyl*cyclo*hex-2-enol (38 g.), and concentrated hydrochloric acid (0·2 c.c.) was set aside under nitrogen for 3 days, then neutralised with potassium carbonate (1 g.) and distilled through a Fenske column. The *ether* (48 g., 78%) had b. p. 82—83°/10^{-4} mm., n_D^{25} 1·5022, $\lambda_{max.}$ (in EtOH) 2260 Å (ε 12,000), $\nu_{max.}$ 3290 (≡C–H), 3021 (=C–H), 2933 and 2882 (C–H), 2110 (C≡CH), 1626 (C=C) cm.$^{-1}$ (Found: C, 76·05; H, 9·3. $C_{14}H_{20}O_2$ requires C, 76·3; H, 9·15%).

4-Chloro-6 : 7 : 8 : 9-tetrahydro-8-methyl-1-(1 : 4 : 5-trimethylhex-2-enyl)indane.—Ergocalciferol (5 g.) was oxidised by Dimroth and Jonsson's method [9] to the C_{19} *ketone*, b. p. 150—174° (bath)/10^{-4} mm., n_D^{25} 1·4942 (Found: C, 81·4; H, 11·5. $C_{19}H_{32}O$ requires C, 82·5; H, 11·7%) (no analysis or physical constants have previously been recorded). Another preparation,

purified by chromatography in benzene on alumina, had n_D^{25} 1·4945 (Found: C, 82·8; H, 11·8%). It gave a 2 : 4-*dinitrophenylhydrazone*, orange needles (from aqueous methanol), m. p. 86—89°, $\lambda_{max.}$ (in $CHCl_3$) 3680 Å (ε 21,000) (Found: 66·2; H, 8·2; N, 11·8. $C_{25}H_{36}O_4N_4$ requires C, 65·8; H, 8·0; N, 12·3%).

The C_{19} ketone (1·8 g.) in dry ether (5 ml.) was added dropwise (3 hr.) to phosphorus pentachloride (1·8 g.) suspended in dry ether (5 ml.) at 0°.[16] After 16 hr. at room temperature, the mixture was poured on crushed ice, stirred for 2 hr., and extracted with ether. Concentration of the washed and dried extracts gave an oil (1·5 g.) which was transferred in benzene to an alumina column and eluted with light petroleum (b. p. 60—80°). The product (0·7 g.), isolated from the first 55 c.c. of eluate, was twice re-chromatographed in light petroleum (b. p. 60—80°) to give the *chloro-hydrocarbon* (0·4 g.), n_D^{24} 1·5045 (Found: C, 77·2; H, 10·65; Cl, 12·2. $C_{19}H_{31}Cl$ requires C, 77·4; H, 10·6; Cl, 12·0%), $\lambda_{max.}$ (in hexane) 1900 Å (ε 17,500).

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Department of Chemistry,
Imperial College of Science and Technology,
South Kensington, London, S.W.7. [*Received, May 19th*, 1958.]

[16] Cf. Braude and Coles, *J.*, 1950, 2014.

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679. *Fading and Tendering Activity in Anthraquinonoid Vat Dyes. Part IV.*[1] *Polarographic Oxidation of* leuco-*Dyes.*

By C. J. Cooper and H. I. Stonehill.

Polarographic oxidation of the *leuco*-solutions in 48% aqueous ethanol of 12 anthraquinonoid vat dyes, some of which exhibit fading and tendering activity, was studied at 25° at pH 11·15—12·88. Most of the dyes give adsorption waves. Three give a single diffusion wave corresponding to one-step oxidation of quinol to quinone. Four others give in addition another of different height, at more positive potentials, ascribed to bivalent oxidation of the tautomeric oxanthranol. Two others give two such additional waves, ascribed to bivalent oxidations of some anthrone and anthranol formed by over-reduction of the oxanthranol during vatting. The three remaining dyes give two diffusion waves of approximately equal height, probably due to bivalent oxidations of quinol and oxanthranol, as for four other dyes. Comparison with potentiometric data indicates that polarography is incapable of revealing the formation of relatively stable semiquinones by many of these dyes. There is no obvious relation between half-wave potentials for quinol oxidation and tendering activity, although more negative values tend to be associated with fading. Intense irradiation of the *leuco*-solutions in the region of the dropping-mercury electrode with visible light, even in the presence of potential mediators, or with *X*-rays, is without effect on the polarograms; this contrasts with the effect during potentiometric titration of tendering-active dyes.

Since fading and tendering phenomena are associated with oxidation or reduction of a photoactive dye,[1] the redox characteristics of the dye, in particular the stability of a semiquinone, may be involved in determining the efficiency of photosensitisation. Potentiometric examination of the redox characteristics of anthraquinonoid vat dyes is rendered difficult by their low solubility in water. Geake and his co-workers [2] determined the redox potentials and semiquinone formation constants of some of such dyes by potentiometric oxidative titration of their *leuco*-solutions in aqueous organic solvents, mainly

[1] Part III, Moran and Stonehill, *J.*, 1957, 788.

[2] (*a*) Geake and Lemon, *Trans. Faraday Soc.*, 1938, **34**, 1409; (*b*) Appleton and Geake, *ibid.*, 1941, **37**, 45; (*c*) *Idem*, *ibid.*, p. 60.

50% pyridine. Gupta [3] and Marshall and Peters [4] similarly obtained the redox potentials of acid *leuco*-dyes in anhydrous pyridine, but in the absence of data on the dissociation constants of the *leuco*-acids, it is impossible to relate these potentials to those obtained in alkaline media. Waly, Preston, Scholefield, and Turner [5] carried out potentiometric redox titrations of aqueous suspensions of vat-dyed cotton, using potential mediators to ensure electrode equilibrium. They observed a constant potential during the major part of each titration, due to dye insolubility. For tendering dyes only, this constant potential was shifted to more negative values upon illumination; a similar but smaller shift occurred for aqueous suspensions of such dyes without cotton. Hadfield [6] could not reproduce these potential shifts, apart from a slight effect when traces of oxygen were present. Waly *et al.*[5] ascribed the shift to change in either the chemical nature or the solubility of the dye or its *leuco*-derivative. Turner [7] later suggested that the cause was a very active unidentified species produced during reduction of the dye.

The present paper describes an attempt to investigate the redox behaviour of some anthraquinonoid vat dyes by polarography, which has been used in a similar study of other types of dye [8] and of simple anthraquinone derivatives.[9] The possibility of a polarographic analogue of the potential shifts mentioned above was also investigated. During the work, photochemical dehalogenation of certain *leuco*-dyes was observed; the following paper records a study of this phenomenon.

Although anthraquinone has been polarographically reduced in solution in aqueous dioxan,[10] *NN*-diethylformamide,[11] and aqueous methanol,[12] as well as while solubilised in aqueous chloroform with wetting agents,[13] attempts to reduce polarographically Caledon Gold Orange G dissolved in anhydrous dioxan and pure or aqueous ethanol failed, essentially because of low dye-solubility. Attention was therefore confined to the polarographic oxidation of *leuco*-dyes in 48% aqueous ethanol, the ethanol being included to facilitate catalytic reduction of the dyes.

Experimental

Materials.—The dye samples were purified by Moran and Stonehill's method.[14] Algol Yellow WG (1-benzamidoanthraquinone) thus prepared was yellow-brown and gave abnormally small polarographic diffusion currents, suggesting the presence of an impurity. This dye was therefore synthesised from recrystallised 1-aminoanthraquinone at the lowest practicable temperature, washed with sodium hydroxide solution, water, and ethanol, and twice recrystallised from xylene (yellow needles). The anthanthrone used was a small commercial sample (Imperial Chemical Industries Limited, Dyestuffs Division), recrystallised from chlorobenzene. The dyes were used as standard 0·1% or 0·2% suspensions in 50% aqueous ethanol, prepared by grinding the dyes with water to a smooth paste with the aid of a palette knife and glazed tile, and then diluting them suitably.

Buffers were prepared from " AnalaR " carbonate-free sodium hydroxide, disodium hydrogen phosphate, and boric acid, with sufficient " AnalaR " potassium chloride to give a final ionic strength of 0·1. Their pH values in water and apparent pH values in 48% aqueous ethanol, determined with the Cambridge pH meter and " Alki " glass electrode, were:

Buffer	0·1N-NaOH	Phosphate	Phosphate	Borate
pH in water	12·70	11·80	10·93	10·13
pH in 48% ethanol	12·88	12·12	11·56	11·15

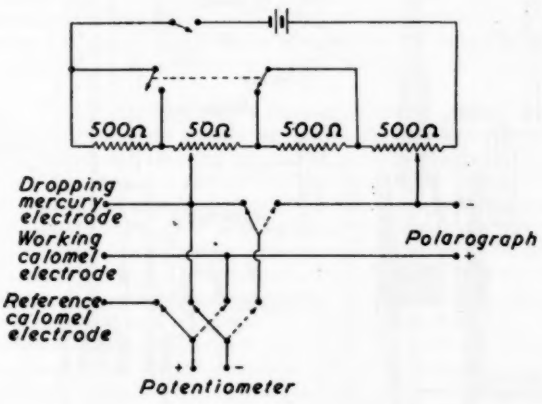
[3] Gupta, *J.*, 1952, 3479.
[4] Marshall and Peters, *J. Soc. Dyers and Colourists*, 1952, **68**, 289.
[5] Waly, Preston, Scholefield, and Turner, *ibid.*, 1945, **61**, 245.
[6] Hadfield, M.Sc. (Tech.) Thesis, Manchester, 1948.
[7] Turner, *J. Soc. Dyers and Colourists*, 1949, **65**, 637.
[8] Kaye and Stonehill, *J.*, (*a*) 1951, 27; (*b*) 1951, 2638; (*c*) 1952, 3231, 3244.
[9] Gill and Stonehill, *J.*, 1952, (*a*) 1845, (*b*) 1857.
[10] Furman and Stone, *J. Amer. Chem. Soc.*, 1948, **70**, 3055.
[11] Edsberg, Eichlin, and Garis, *Analyt. Chem.*, 1953, **25**, 798.
[12] Vainshtein, *Zavodskaya Lab.*, 1949, **15**, 411.
[13] Proske, *Analyt. Chem.*, 1952, **24**, 1834.
[14] Moran and Stonehill, *J.*, 1957, 765.

XUM

Sodium dithionite (Brotherton and Co. Ltd.) was of 98—99% purity. The ethanol was redistilled absolute alcohol. Mercury for polarography was treated with permanganate solution, sprayed through mercurous nitrate solution, washed with water, and vacuum-distilled three times. Raney nickel was prepared according to Vogel's directions [15] and stored under absolute alcohol. It retained its activity for several weeks, but then deteriorated rapidly. A suitable volume of the well-shaken suspension was pipetted out as required. Platinised and palladised asbestos (5%) were commercial samples. Hydrogen (from a cylinder) was rigorously deoxygenated by passage through a Baker Platinum "Deoxo" catalyst unit, followed by a Pyrex tube packed with palladised asbestos and heated to about 400° by a tubular electric heater. The "Deoxo" unit was at first used at room temperature, but in later work it was kept at about 100° by means of an Exothermal electric heating tape wound around it.

Apparatus.—Polarograms were obtained by means of a Tinsley Recording Polarograph, Model V 3211. Since the fixed voltage scanning speed of this instrument, 0·5 v/min., was too fast for accurate determination of wave-forms and potentials, it was reduced 5-fold by similarly

FIG. 1.



reducing the potential across the polarograph potentiometer by means of a 1500-ohm 2-watt wire-wound series resistor in the battery circuit, this resistor being put out of circuit when normal scanning speed was desired. An additional effect of the resistor was the reduction of the potential span of the polarograph potentiometer from the normal range of +0·5 to −3·0 v, to the narrow range +0·1 to −0·6 v. In order to permit a wider span, an auxiliary voltage-dividing potentiometer was inserted between the polarograph and the cell to provide a biassing voltage. With this circuit, shown in Fig. 1, voltages within the ranges 0—1 or 1—2 could be tapped off, depending on which 500 ohm resistor were put out of circuit. Thus the polarographic potential span was 0·7 v situated anywhere between the limits +0·1 and −2·6 v. Voltages supplied by the polarograph together with the auxiliary potential divider were measured with a Pye Precision Potentiometer, which also served to determine the potential of the dropping-mercury electrode against a reference saturated calomel electrode carrying no current, in order to correct for ohmic potential drop across the cell.

Since the d. c. amplifier of the polarograph was unidirectional in operation, a large counter-current zero correction was required when the polarograph was used for oxidative (anodic) polarography and the applied voltage sweep was in the normal direction, towards increasingly negative values, in order that the polarographic zero current should correspond to maximum recorder-galvanometer deflection. Under these conditions the recorder deflection was no longer linearly related to cell current, as it was when zero cell current corresponded to only a small recorder deflection. To overcome this difficulty, the polarity of the polarograph potentiometer was reversed for oxidative polarography, as were the cell electrode connections. This

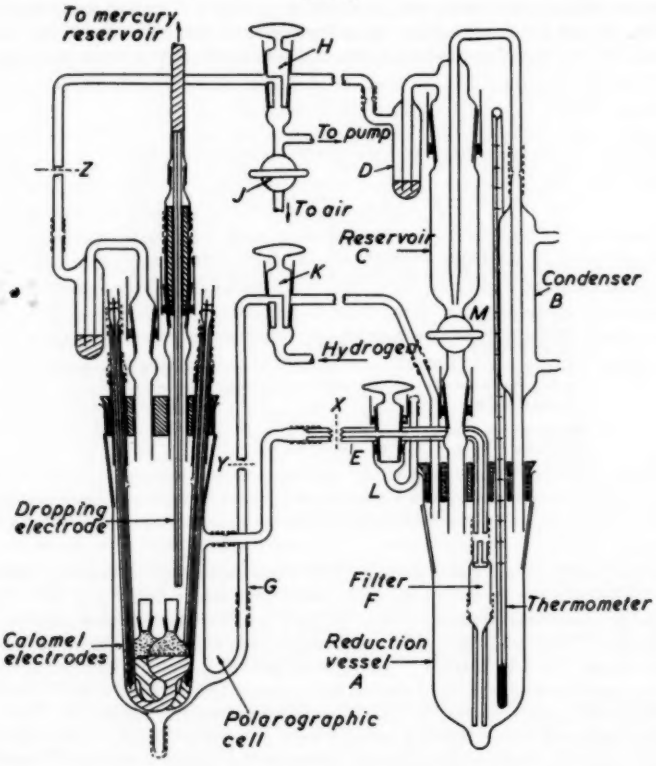
[15] Vogel, "Textbook of Practical Organic Chemistry," Longmans, Green and Co., London, 1948.

also necessitated reversing the polarity of the auxiliary and built-in standardising potentiometers. To facilitate this polarity reversal an 8-pole 2-way switch was used, permitting ready adjustment of the instrument for either oxidative or reductive polarography.

The ratio of successive current sensitivities provided by the polarograph, generally 2, was found to be too great for optimum use of the rather small chart width. The recorder galvanometer was therefore shunted to permit the sensitivity to be changed by factors of $\frac{3}{4}$ or $\frac{2}{3}$ as required.

Polarography and reduction were carried out in separate vessels, shown in Fig. 2, since heating was necessary during reduction. Pyrex glass was used throughout, except for the

FIG. 2.



tubes carrying the external connections to the calomel electrodes, which were of soda glass into which platinum wire contacts were sealed. Flexible connections between glass tubes (broken lines in Fig. 2) were of poly(vinyl chloride) tubing. Water-jacketed condenser *B* condensed any ethanol vaporised during reduction of the dye in vessel *A*. Mercury-bubbler *D* isolated vessel *A* from the air. Reservoir *C* contained liquids (*e.g.*, acid buffer components) whose presence might interfere with the catalytic reduction of the dye in *A*; such liquids were added to the *leuco*-solution, after reduction, *via* tap *M*. Filter *F*, packed with glass wool, prevented catalyst from being carried over with *leuco*-solution during its transfer from *A* through tap *L* to the polarographic cell. Taps *H*, *K*, *L* and all ground-glass joints, other than those of which vessel *A* and the polarographic cell were constructed, were fitted with water seals.

The polarographic cell assembly was similar to that of Kaye and Stonehill;[8a] this type was considered more convenient than the usual H-type cell for evacuation, rigorous exclusion of air, and cleaning. The cathode was a dip-type saturated calomel electrode. A second similar

electrode, which carried no current, permitted determination of the dropping-mercury electrode potential without errors due to ohmic potential drop. The calomel electrode vessels had a small hole in the main stem, above the liquid level, to permit equalisation of internal and external pressures during removal of air from the cell by evacuation, and also to permit thorough degassing of the electrode contents by evacuation after filling, thus preventing the formation of a high-resistance layer of gas bubbles underneath the small glass stopper. The electrodes, after being filled and degassed, were kept for 24 hr. before use. After each experiment they were washed externally with distilled water and, after their stoppers had been loosened, were immersed in distilled water until next required. Their potentials were periodically checked against each other and against a third electrode, and when, infrequently, they differed by 2 mv or more, the electrodes were refilled. When the polarographic cell resistance, calculated from the ohmic potential drop, rose significantly above the usual 5000 ohms, the glass stoppers of the electrodes were thoroughly flushed with the potassium chloride solution, which was replenished if necessary.

The polarographic cell was immersed in a well-stirred thermostatic water-bath, kept at 25° ± 0·02° by means of a metal 250-w immersion heater (to avoid photolytic effects of light bulbs), mercury–toluene thermoregulator, and electronic relay. The dye-reduction vessel was heated by immersion in a small water-bath (a 250 ml. glass crystallising dish) on an electric hot-plate controlled by a Simmerstat and three-heat switch. This bath was fitted with a cold water inlet and an overflow, to permit rapid cooling of the *leuco*-solution before transfer to the polarographic cell.

Reduction of Dyes.—Preliminary work on the reduction of Caledon Gold Orange G and Caledon Orange 2RTS with alkaline sodium dithionite showed that excess of dithionite was required for complete reduction, that the *leuco*-dyes gave polarographic oxidation waves at about −0·7 v (against the saturated calomel electrode), and that, in agreement with earlier work,[9a] alkaline dithionite alone gave anodic waves in the same potential region. It was thus necessary to remove excess of dithionite to avoid interference with the dye waves. Attempts to do so by adding measured amounts of formaldehyde solution or by bubbling in known volumes of air were unsuccessful; formaldehyde addition caused a new wave to appear at about −0·4 v; addition of air was difficult to control and probably caused some oxidation of *leuco*-dye. Further work was thus restricted to catalytic dye reduction. Preliminary tests with Raney nickel and Caledon Gold Orange G (one of the most difficult dyes to reduce) showed that a high reduction temperature is desirable, that reduction takes at least 30 min. for low dye concentrations and longer for higher concentrations, that it is facilitated by increasing the pH and by addition of ethanol, at least 8% of the latter being necessary, and that the catalyst is more effective if added before than after displacement of air from the system by hydrogen.

Freshly prepared nickel catalyst caused over-reduction of some dyes. Thus Caledon Orange 2RTS gave a solution which changed during reduction from the purple colour obtained by dithionite reduction to a dichroic orange; this, unlike the normal purple *leuco*-solution, became colourless on reoxidation with hydrogen peroxide and would not then give a coloured solution on reduction by dithionite. Although the over-active catalyst could be sufficiently deactivated by bubbling air through it for some minutes, the necessary re-evaluation of the deactivated catalyst was tedious. In such cases, therefore, a platinised or, better, a palladised asbestos catalyst proved suitable. However, some samples of these catalysts caused dehalogenation of some dyes: as no simple deactivation process was available for these catalysts, nickel catalysts were used for reducing these dyes. Each batch of nickel catalyst was tested for over-activity by reducing the halogenated dye Caledon Orange 2RTS with a sample for 1½ hr. at 70° and examining the solution polarographically for any shift of half-wave potential. No indication of partial dehalogenation was ever observed; a given batch of catalyst gave, according to its activity, a solution which yielded polarograms characteristic either of the undehalogenated dye or of its completely dehalogenated analogue, but never of both together.

Procedure.—A high ethanol concentration in the *leuco*-solution minimises adsorption effects on polarograms,[8] but causes precipitation of buffer salts; a compromise concentration of 48% ethanol was thus adopted. By postponing the addition of water or aqueous solution of acid buffer components until after reduction, the latter was facilitated by the availability of higher ethanol concentrations and higher pH.

A measured volume of well-shaken dye suspension was placed in reduction vessel *A* (Fig. 2), together with suitable quantities of ethanol, sodium hydroxide solution, catalyst, and water.

XUM

The required quantity of water or aqueous solution of acidic buffer component was placed in reservoir *C* together with a little catalyst, and the apparatus assembled. The reduction apparatus and the polarographic cell were isolated from each other by means of taps *H*, *K*, and *L*, and separately evacuated. Hydrogen was then passed in through the cell and thence through tap *L* into the reduction vessel until these were at atmospheric pressure, as indicated by a manometer in the vacuum-pump line. After a second evacuation and flushing with hydrogen, mercury-bubbler *D* was connected to the air by taps *H* and *J*, and hydrogen was slowly bubbled *via* filter *F* through the contents of the reduction vessel until dye reduction was complete (1—1½ hr.). Reduction temperatures were 45—50° for anthanthrone and Cibanone Golden Yellow GK, 50—55° for Cibanone Golden Yellow RK, 55—60° for Algol Yellow WG, Caledon Red X5BS, Cibanone Brilliant Orange GK, and Caledon Brilliant Orange 4RN, 60—65° for Caledon Red 5G, Caledon Brilliant Orange 6R, Caledon Orange 2RTS, and Caledon Blue RC, and 70—75° for Caledon Gold Orange G. The contents of reservoir *C* were then slowly added to the reduction vessel, which was cooled by filling the heating-bath with cold water. Tap *M* was closed, and tap *H* turned to connect the bubbler outlet from the cell to the air. Hydrogen was then passed through tap *K* directly into the reduction vessel, thus forcing the *leuco*-solution into the cell through filter *F*.

A preliminary polarogram was recorded with the 0·5 v/min. scanning speed and extended voltage sweep (−0·5 to −3·0 v), in order to determine the requisite voltage range and permit the adjustment of galvanometer zero, sensitivity, and counter-current. The cell was then disconnected, the voltage across the polarograph potentiometer reduced to 0·7 v, and the necessary biassing voltage applied with the auxiliary potential divider. The cell was then re-connected, any necessary zero-current adjustments made, and a polarogram recorded at the reduced voltage-scanning rate. At intervals of 0·1 v in the applied potential, the potential of the dropping-mercury electrode was measured to within 1 mv against the reference calomel electrode. From the linear graph of cell current against correction to the applied potential for ohmic drop across the cell, the correction for any given applied potential could be determined.

Polarograms were determined at mercury column heights, *h*, of 70, 58, 46, and 35 cm., and the slope of the graph of log *i* (*i* = wave-height) against log *h* was determined for each wave. Theoretically slopes of 0·5, 1·0, and 0—0·5 denote respectively diffusion, adsorption, and kinetic waves. In practice, slopes between 0·35 and 0·65 were assumed to correspond to diffusion waves, and higher and lower values to adsorption and kinetic waves respectively.

Since the *leuco*-solutions of some halogenated dyes underwent dehalogenation and oxidation on exposure to visible light, the reduction apparatus and polarographic cell were housed in a small light-tight cabinet.

For investigating the effect of irradiation on the polarograms, the micro-polarographic cell described elsewhere[16] was used. This permitted maximum irradiation of the dropping-mercury electrode surface region, in which the redox system is located in polarography, since a minimum thickness of *leuco*-solution was interposed between it and the radiation source. *leuco*-Solutions in 48% ethanol containing 0·1N-sodium hydroxide, prepared by hydrogen–nickel reduction, were transferred to the cell by the normal technique,[16] the whole operation being in the dark. The maximum possible volume of solution was retained in the cell to minimise concentration decrease due to electrolysis during polarography. Polarograms were recorded first in the dark, and then at 15 min. intervals during irradiation of the dropping-electrode surface region with a 300-w projection lamp giving a condensed beam 1½ in. in diameter, or with *X*-rays from a General Electric Model D portable *X*-ray generator. No corrections were made for ohmic potential drop, since only comparative results were required. The experiments with visible light were repeated with solutions to which 1 ml. of a 50% ethanolic solution of a mixture of potential mediators was added after reduction but before transfer to the cell. The mediator solution was 0·001M with respect to each of Methylene Blue, potassium indigotetrasulphonate, potassium indigodisulphonate, 1-aminoanthraquinone-8-sulphonic acid, sodium anthraquinone-2-sulphonate, 1-amino-4-bromoanthraquinone-2-sulphonic acid, 3-amino-anthraquinone-2-sulphonic acid, and 1 : 2-dihydroxyanthraquinone.

Results

Because of the difficulty in preparing homogeneous dye suspensions and achieving complete reduction, the frequent multiplicity and poor definition of the waves, and the small recorder

[16] Cooper and Stonehill, *J.*, 1958, 3362.

chart-width, the accuracy of the recorded data is limited in some cases to about 10% in wave-heights and 10 mv in half-wave potentials. The pH range employed was limited by precipitation of acid *leuco*-dye at lower pH values. The detailed polarographic results are given in Table 1, where A to E refer to the successive waves in order of increasingly negative $E_{\frac{1}{2}}$ given by a particular dye.

Algol Yellow WG gave two diffusion waves, A (partly kinetic) and B, with wave-height ratio A/B tending to about 1·15 at higher concentrations, independent of pH.

Caledon Red 5G gave, when reduced with a partially deactivated nickel catalyst, a cathodic wave at about −0·9 v, in addition to two anodic waves. Since the cathodic wave suggested incomplete reduction, fresh fully active nickel catalyst was used in subsequent experiments. This resulted in three anodic diffusion waves, A, B, and C, with the same total height as the former cathodic plus two anodic waves. The height of C is independent of pH, while the height ratio B/A varies considerably with pH.

Caledon Red X5BS, like the preceding dye, required fresh nickel catalyst for complete reduction, and gave three diffusion waves, an additional small adsorption wave appearing at pH 12·88.

Anthanthrone, although not strictly a dye because of its low affinity for cellulose, was of interest as the parent compound of Cibanone Brilliant Orange GK and Caledon Brilliant Orange 6R. Two diffusion waves, A and B, were observed at all pH values; B is complicated by a small maximum no suppressed by 0·1% of gelatin, methylcellulose, or Methyl Red. The wave-height ratio A/B (the maximum being ignored) rises as pH falls.

Cibanone Brilliant Orange GK gave two diffusion waves, A and C; the latter had an associated adsorption after-wave D at pH 12·88, and an adsorption fore-wave B at lower pH. At any given pH, the wave-height ratio of C plus B or D to A varies with rise of concentration, tending to a limit of ~1.

Caledon Brilliant Orange 6R gave two diffusion waves, B, with an adsorption fore-wave A, and D, with an adsorption after-wave E at pH 12·88 and an adsorption fore-wave C at lower pH. The ratio of the heights of the diffusion waves, each together with its adsorption wave, varies with rise of concentration, tending to a limit of ~1.

Caledon Gold Orange G was difficult to reduce, requiring freshly prepared nickel catalyst at 70—80°. At all pH values a polarographic maximum was observed, not removable by adding various suppressors, although 0·01% of gelatin improved the wave form and was thus added throughout. A single diffusion wave C was observed, preceded at pH 12·88 and 12·12 by an adsorption wave B; at lower pH the latter split into two ill-defined steps A and B, similar to those reported for acridine.[82]

Both Caledon Orange 2RTS and Caledon Brilliant Orange 4RN gave two diffusion waves, B and D. Each was associated with an adsorption fore-wave, A and C respectively, the latter occurring at pH 12·88 only. The wave-height ratio (A + B)/C + D) decreases with rise of concentration at constant pH, or with rise of pH at constant concentration.

Cibanone Golden Yellow GK gave a single diffusion wave with a maximum unaffected by 0·1% of gelatin, methylcellulose, or Methyl Red. At pH 12·88 the maximum was only slight, being indicated mainly by erratic galvanometer oscillations, but at lower pH it occurred as a broad hump. At pH 12·88 the polarograms were unsymmetrical, being drawn out at the more negative potentials, especially at lower concentrations. In Table 1, both maximum and minimum values of wave-heights are quoted.

Cibanone Golden Yellow RK gave at pH 12·88 two diffusion waves, B and C. As pH was decreased, the relative height of B fell until at pH 11·56 or below only C remained. An adsorption after-wave D occurred at pH 12·88, and an adsorption fore-wave A at lower pH.

Caledon Blue RC, the only halogenated dye examined which did not become dehalogenated when irradiated or electrolysed in *leuco*-solution, was not investigated at pH below 12·12 because of precipitation of the *leuco*-acid. It gave a single diffusion wave B, preceded at pH 12·12 only by an adsorption wave A.

In the study of the effect of irradiation on the polarograms of *leuco*-dyes, use was made of Caledon Gold Orange G, Cibanone Golden Yellow GK, Caledon Red 5G, and Caledon Blue RC. The first three are highly active, the last inactive, in tendering.[17,18] Apart from the last, they

[17] Landolt, *J. Soc. Dyers and Colourists*, 1949, **65**, 659.
[18] Fox, *ibid.*, p. 508.

XUM

TABLE 1. *Half-wave potentials* vs *saturated calomel electrode and wave-heights.*

pH	c (mM)	$-E_{\frac{1}{2}}$ (mv) A	B	C	D	E	i (μA) A	B	C	D	E
Algol Yellow WG; m = 3·207 mg./sec., t = 2·61 sec.; A kinetic-diffusion; B diffusion											
12·88	0·29	626	785				0·76	0·78			
,,	0·67	647	787				2·10	1·50			
,,	1·15	676	789				3·45	2·70			
12·12	0·48	626	779				1·29	1·17			
,,	0·96	669	769				2·51	2·34			
11·56	0·48	635	735				1·38	1·20			
,,	1·05	659	739				3·06	2·46			
11·15	0·48	630	732				1·20	1·15			
,,	0·96	651	737				2·76	2·28			
Caledon Red 5G; m = 3·310 mg./sec., t = 2·53 sec.; A, B, C diffusion											
12·88	0·70	402	535	731			1·28	0·24	1·24		
,,	1·40	409	532	728			1·95	0·68	2·62		
12·12	0·70	348	482	733			0·30	0·72	1·44		
,,	1·40	335	473	730			0·97	1·80	2·70		
11·56	0·70	327	458	697			0·51	0·60	1·29		
,,	1·40	307	448	690			1·26	1·62	2·16		
11·15	0·70	320	460	726			0·56	0·68	1·48		
,,	1·40	310	453	705			1·27	1·60	2·53		
Caledon Red X5BS; m = 3·286 mg./sec., t = 2·55 sec.; A, B, C diffusion; D adsorption											
12·88	0·55	513	645	761	892		0·27	0·56	1·01	0·27	
,,	1·22	519	637	770	879		0·53	1·23	2·19	0·58	
12·12	0·55	498	652	758			0·72	0·56	0·80		
,,	1·22	471	661	760			1·12	1·44	1·71		
11·56	0·55	458	663	769			0·56	0·56	0·83		
,,	1·11	449	648	764			0·75	1·33	1·82		
11·15	0·55	461	661	762			0·40	0·56	0·85		
,,	1·00	470	656	769			0·72	1·24	1·56		
Anthanthrone; m = 3·139 mg./sec., t = 2·67 sec.; A, B diffusion											
12·88	0·24	598	707				0·72	0·60			
,,	0·59	596	704				1·76	1·16			
,,	0·99	602	708				3·12	2·10			
12·12	0·48	605	705				1·72	1·00			
11·56	0·48	604	688				1·76	0·80			
11·15	0·24	599	688				0·80	0·33			
,,	0·48	603	696				1·80	0·60			
,,	0·95	600	687				3·60	1·47			
Cibanone Brill. Orange GK; m = 3·170 mg./sec., t = 2·64 sec.; A, C diffusion; B, D adsorption											
12·88	0·21	500		667			0·14		0·23		
,,	0·53	506		664	685		0·51		0·36	0·28	
,,	1·07	506		668	691		1·04		0·72	0·51	
,,	1·60	508		670	707		1·80		1·55	0·55	
,,	2·13	506		674	706		2·44		2·00	0·50	
,,	2·67	505		671	711		3·18		2·81	0·55	
12·12	0·53	548	610	647			0·71	0·30	0·35		
,,	1·21	551	618	652			1·52	0·36	1·04		
11·56	0·53	558	614				0·75	0·44			
,,	1·33	567	608	642			1·68	0·68	0·92		
11·15	0·40	553	614				0·71	0·41			
,,	1·21	565	612	636			1·52	0·64	0·74		
Caledon Brill. Orange 6R; m = 3·139 mg./sec., t = 2·67 sec.; B, D diffusion; A, C, E adsorption											
12·88	0·67	497	530		670	718	0·24	0·93		0·72	0·57
,,	1·35	504	531		676	726	0·30	1·98		1·92	0·60
12·12	0·40	488	530	610	647		0·06	0·58	0·30	0·35	
,,	1·48	539		655			2·40		2·56		
11·56	0·67	465	559	608	649		0·19	0·96	0·48	0·56	
,,	1·21	450	559	603	651		0·27	1·87	0·43	1·63	
11·15	0·27	470	553	612			0·21	0·34	0·32		
,,	1·35	480	563	602	648		0·27	2·08	0·48	1·68	

TABLE 1. (*Continued.*)

pH	c (mM)	$-E_{\frac{1}{2}}$ (mv) A	B	C	D	E	i (μA) A	B	C	D	E
Caledon Gold Orange G; m = 3·103 mg./sec., t = 2·70 sec.; C diffusion; A, B adsorption											
12·88	0·49		731	785				0·42	0·92		
,,	0·82		773					2·34			
12·12	0·33		712	756				0·18	0·72		
,,	0·41	—	706	753				0·17	0·97		
,,	0·82		704	762				0·15	2·28		
11·56	0·16	674	717				0·17	0·37			
,,	0·33	636	698	735			0·12	0·41	0·37		
,,	0·49	653	707	744			0·12	0·46	0·84		
,,	0·82	696		746			0·60		1·68		
11·15	0·41	664	733	754			0·20	0·45	0·48		
Caledon Orange 2RTS; m = 3·139 mg./sec., t = 2·67 sec.; B, D diffusion; A, C adsorption											
12·88	0·19	559	611	641	690		0·09	0·04	0·09	0·05	
,,	0·28	559	602	642	699		0·16	0·07	0·13	0·15	
,,	0·37	549	610	659	702		0·19	0·16	0·13	0·27	
,,	0·47	555	602	689			0·22	0·30	0·53		
,,	0·93	539	600	692			0·16	0·68	0·96		
,,	1·21	535	600	705			0·15	1·02	1·41		
,,	1·86	606		708			1·81		2·29		
12·12	0·58	524	633		700		0·22	0·88		0·46	
,,	1·16	530	643		710		0·33	1·47		0·84	
11·56	0·81	492	635		705		0·18	1·02		0·60	
,,	1·16	494	630		700		0·27	1·41		0·90	
11·15	0·70	496	631		704		0·18	0·90		0·36	
,,	0·93	499	634		714		0·21	1·46		0·45	
,,	1·39	494	638		719		0·24	1·76		0·68	
Caledon Brill. Orange 4RN; m = 3·139 mg./sec., t = 2·67 sec.; B, D diffusion; A, C adsorption											
12·88	0·22	518	547	618	682		0·09	0·06	0·08	0·21	
,,	0·36	513	563	609	680		0·10	0·12	0·07	0·51	
,,	0·49	518	560	605	687		0·11	0·15	0·06	0·67	
,,	0·90	519	565		692		0·10	0·44		1·22	
,,	1·17	492	560		684		0·12	0·54		1·71	
12·12	0·36	488	582		693		0·12	0·32		0·24	
,,	0·72	500	577		696		0·13	0·68		0·56	
,,	1·26	492	590		693		0·15	1·26		1·20	
11·56	0·36	452	580		691		0·10	0·34		0·30	
11·15	0·36	447	591		686		0·08	0·31		0·22	
,,	0·72	454	586		692		0·11	0·67		0·51	
Cibanone Golden Yellow GK; m = 3·139 mg./sec., t = 2·67 sec.; A diffusion											
12·88	0·19	673					0·69				
,,	0·47	663					1·66				
,,	1·32	668					4·70				
12·12	0·47	672					1·40,[a] 1·56[b]				
11·15	0·47	658					1·38,[a] 1·54[b]				
,,	0·94	664					2·86,[a] 3·27[b]				
Cibanone Golden Yellow RK; m = 3·139 mg./sec., t = 2·67 sec.; B, C diffusion; A, D adsorption											
12·88	0·31		630	693				0·44	0·37		
,,	0·61		621	665	719			0·82	0·46	0·36	
,,	1·02		623	669	718			1·52	0·88	0·40	
,,	1·53		620	674	726			2·13	1·55	0·37	
,,	1·94		619	683	738			2·80	2·40	0·34	
,,	2·35		612	678	738			3·45	2·84	0·37	
12·12	0·64	502	618	654			0·06	0·52	1·30		
,,	1·28	518	619	666			0·05	1·12	2·61		
11·56	1·28	524		656			0·20		3·12		
11·15	0·38	534		648			0·15		0·83		
,,	1·28	517		656			0·16		3·48		
Caledon Blue RC; m = 3·192 mg./sec., t = 2·70 sec.; A adsorption; B diffusion											
12·88	0·50		693					1·11			
,,	0·75		686					1·64			
12·12	0·50	574	677				0·17	1·01			
,,	1·25	564	686				0·12	2·72			

[a] Minimum value; [b] maximum value.

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are unhalogenated and, unlike the other halogenated dyes in Table 1, do not undergo photo-oxidation in *leuco*-solution. (It is indeed surprising that Waly *et al.*[5] did not mention this photo-reaction which must have occurred during irradiation of various halogenated *leuco*-dyes they investigated.) Two concentrations were used for each dye, *viz.*, the highest which permitted observation of the dropping electrode, and the lowest which gave well-defined, reproducible waves. No change was observed in the polarograms of any of four dyes after irradiation with visible light for 1 hr., or for the first two dyes after exposure to *X*-rays for ½ hr. Similar negative results were obtained on exposing all four *leuco*-dyes to visible light in the presence of the mixed potential mediator, which was of the same composition and used with similar concentrations of dye and mediator as in the work of Waly *et al.*[5] The small relative amount of mediator used was found to have a negligible effect on the dye polarograms in the dark.

Discussion

In Table 2 are listed, for all the dyes examined, the values of the overall diffusion current constant I ($= i_{total}/cm^{2/3}t^{1/6}$), the number of diffusion waves, and the electron-loss per molecule (n) as obtained coulometrically.[16] In all cases I is independent of both c and pH, within experimental error. This argues against dye aggregation, which was suggested by Peters and Sumner [19] as a possible cause of deviations from a thermodynamic theory of adsorption on cotton of *leuco*-dyes at lower concentrations than those concerned here.

Table 2. *Diffusion current constants and coulometric electron losses.*

Dye	No. of main waves	I (overall)	n (electrons per mol.)
Algol Yellow WG	2	2·05	2
Caledon Red 5G	3	1·45	2
Caledon Red X5BS	3	1·39	2
Anthanthrone	2	2·09	2
Cibanone Brilliant Orange GK	2	0·95	1
Caledon Brilliant Orange 6R	2	1·33	1
Cibanone Golden Yellow GK	1	1·40	2
Cibanone Golden Yellow RK	2	1·09	1
Caledon Gold Orange G	1	1·14	2
Caledon Orange 2RTS	2	0·85	1
Caledon Brilliant Orange 4RN	2	0·78	1
Caledon Blue RC	1	0·90	2
Cibanone Blue RSN [18]	1	0·93	2

For the dyes giving a single main wave, n is 2, suggesting a one-stage electro-oxidation of quinol to quinone represented by: $R(O^-)_2 - 2e \longrightarrow RO_2$, the quinol being fully ionised since the $E_{\frac{1}{2}}$ values for the main waves are practically independent of pH over the range studied.

For the dyes giving two main waves, the value of n is 2, except for those dyes which in *leuco*-solution undergo dehalogenation and oxidation in light or upon electrolysis;[16,20] for the latter, the coulometric n-value is 1. However, a comparison of I-values suggests that actually n is 2 for all these dyes, if due allowance is made for the effect of halogenation in increasing molecular size and mass, thus decreasing the diffusion coefficient and I. The I-values for unbrominated Caledon Gold Orange G (1·14) and its di- and tri-bromo-derivatives Caledon Orange 2RTS (0·85) and Caledon Brilliant Orange 4RN (0·78) illustrate this point. The only anomaly is this respect is that I for the bromo-dye Caledon Brilliant Orange 6R is greater than the value for the chloro-analogue, Cibanone Brilliant Orange GK. A possible reason is the greater degree of hydration of the molecule containing the more electronegative chlorine atoms.

The dyes in the two-wave class differ amongst themselves as regards the relative total heights (*i.e.*, including related adsorption waves) of the two main waves and their variation with pH. For Algol Yellow WG, Cibanone Brilliant Orange GK, and Caledon Brilliant Orange 6R, the two wave-heights are approximately equal at all pH values employed. Here the two steps may represent successive one-electron oxidations *via* the semiquinone.

[18] Peters and Sumner, *J. Soc. Dyers and Colourists*, 1957, **73**, 12.
[20] Cooper and Stonehill, following paper.

For anthanthrone, Caledon Orange 2RTS, and Caledon Brilliant Orange 4RN, the total height of the wave with more positive $E_{\frac{1}{2}}$ is greater than that of the other wave, except at pH 12·88 for the last two halogenated dyes, and increases relatively as pH falls. The sum of the two total wave-heights per unit c, however, is independent of pH. Unequal wave-heights could arise from distortion due to polarographic maxima, difference in diffusion coefficients of quinol and semiquinone due to aggregation or complexing with buffer, or limited solubility of quinol or semiquinone. For any of these, pH variation would affect not only the wave-height ratio but also the overall wave-height, contrary to observation.

Pyruvic acid gives on polarographic reduction two waves with pH-dependent height ratio but constant aggregate height.[21] This was explained [22] by ascribing the waves to two different species, the ionised and the un-ionised acid, with different $E_{\frac{1}{2}}$ values, and with relative amounts controlled by a pH-dependent equilibrium whose rate of attainment is slow compared with the electrochemical reduction rate, so that the system is thermodynamically reversible but polarographically irreversible. A similar explanation might apply to the present results, based on the effect of pH variation on either the degree of ionisation of the quinol or the extent of quinol–oxanthrol tautomerisation. The ionisation equilibration is almost certainly too fast to give rise to extra waves, judging from the fact that many anthraquinols under conditions in which they were incompletely ionised gave only a single polarographic wave for a given redox step.[9a] The alternative assumption of a relatively slow quinol–oxanthranol tautomerisation,

$$R(O^-)_2 + 2H^+ \overset{\text{Fast}}{\rightleftharpoons} R(OH)_2 \overset{\text{Slow}}{\rightleftharpoons} O{:}RH{\cdot}OH$$

has been confirmed for certain hydroxyanthraquinols.[9b] Such tautomerism is well known in anthraquinonoid *leuco*-dyes.[23] We may suppose that in polarographic oxidation the oxanthranol wave has a more positive $E_{\frac{1}{2}}$ than the quinol wave, because the quinol is present partly as negative ions; this is supported by a comparison of the $E_{\frac{1}{2}}$ values of the two waves with the $E_{\frac{1}{2}}$ value of a chemically similar molecule which gives only a single (quinol) oxidation wave, *e.g.*, Cibanone Gold Yellow RK compared with Cibanone Gold Yellow GK, or Caledon Orange 2RTS and Caledon Brilliant Orange 4RN with Caledon Gold Orange G. On this basis, the wave-height ratio of quinol to oxanthranol decreases with fall of pH for anthanthrone, Caledon Orange 2RTS, and Caledon Brilliant Orange 4RN, but increases for Cibanone Gold Yellow RK which at pH 11·56 and below gives no oxanthranol wave. The decrease is due to the shift of the tautomerisation equilibrium to the right as pH falls. The increase for the last-mentioned dye may be tentatively ascribed to the faster tautomerisation, which is presumably catalysed by hydrogen ions; when the tautomerisation rates exceed the electro-oxidation rate, the oxanthranol wave disappears. However, it must be mentioned that the rate of tautomerisation of 2-hydroxyanthraquinol is apparently independent of pH.[9b] If these two opposing effects of pH variation on the quinol–oxanthranol wave-height ratio are accepted, they could roughly balance over a limited pH range; this would provide an alternative explanation of the roughly pH-independent wave-height ratio, not quite equal to unity, found for Algol Yellow WG, Cibanone Brilliant Orange GK, and Caledon Brilliant Orange 6R. The partly kinetic nature of the Algol Yellow WG wave at more positive potentials, the parallelism between the $E_{\frac{1}{2}}$ values of both waves for the last two dyes, and for their unhalogenated analogue anthanthrone, and the potentiometric indication (Table 3) that the last dye forms no stable semiquinone, all accord with this view.

Three anodic diffusion waves of unequal heights are given by Caledon Red 5G and Caledon Red X5BS when reduced with an active catalyst, but only two anodic waves and a cathodic wave with a partially deactivated catalyst. The overall coulometric n-value is

[21] Müller and Baumberger, *J. Amer. Chem. Soc.*, 1939, **61**, 590.
[22] Brdicka and Wiesner, *Coll. Czech. Chem. Comm.*, 1947, **12**, 138.
[23] Coffey, *Chem. and Ind.*, 1953, 1068.

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always 2. The cathodic wave occurs at a similar potential (about −0·9 v) to that of the cathodic wave obtained in one experiment with Caledon Red 5G in which catalyst was inadvertently omitted; nevertheless, it is unlikely to be the reduction wave of unreduced dye, since both of these dyes are appreciably soluble in aqueous ethanol and thus readily reduced even with less active catalyst in the cold, and also because the wave-height is approximately proportional to concentration. Now Coffey [23] reported that Caledon Red 5G readily formed an oxanthranol which is easily reduced to the anthrone, and easy reduction of other anthraquinone derivatives to anthrones by sodium dithionite has also been observed.[24] It is thus probable that, with the less active catalyst, the dye quinone is reduced to the quinol and its tautomeric oxanthranol, which account for the two anodic waves, as for the dyes giving only two waves, while the cathodic wave is due to polarographic reduction of oxanthranol to anthrone. With the more active catalyst, it is probable that all the oxanthranol is reduced to the oxanthrone and its tautomeric anthranol

$$O{:}RH{\cdot}OH \xrightarrow{\text{Redn.}} O{:}RH_2 \rightleftharpoons HO{\cdot}R{\cdot}H$$

as fast as it is formed by tautomerisation of the quinol; the *leuco*-solution thus contains quinol, anthrone, and anthranol, which give rise to three anodic oxidation waves. Their aggregate height is proportional to c and independent of pH, but at any given pH their relative heights vary somewhat, probably because of variable extents of oxanthranol formation followed by over-reduction to anthrone and anthranol. Comparison of $E_{\frac{1}{2}}$ values with those of the related benzamidoanthraquinone, Algol Yellow WG, indicates that the wave with the most negative $E_{\frac{1}{2}}$ is due to the quinol. That one of the three oxidisable species in the *leuco*-solution is an impurity is unlikely in view of the relatively large wave-heights observed; nor is it likely to be a hydrolysis product of the dye produced during reduction, since, although these benzamidoanthraquinones are reported to undergo hydrolysis under severe vatting conditions,[18] their appreciable solubility rendered high temperatures unnecessary during reduction.

Appleton and Geake [25] determined potentiometrically the redox potentials, in 0·1N-sodium hydroxide, of three of the dyes concerned here. Although the solvent (50% aqueous pyridine) and temperature (50°) are different, comparison with the present results for the same alkalinity, as in Table 3, is of interest. The first two dyes, and probably also

TABLE 3. *Comparison of potentiometric and polarographic results.*

Dye	Potentiometric standard redox potentials (mv) [a]	Polarographic half-wave potentials (mv) [b]
Caledon Gold Orange G	−564, −616	−780
Cibanone Golden Yellow GK	−490, −658	−668
Caledon Brilliant Orange 6R	−581	−530, −673

[a] In 0·1N-NaOH, 50% aqueous pyridine, 50° (ref. 25). [b] In 0·1N-NaOH, 48% aqueous ethanol, 25°.

the third, give a single 2-electron polarographic wave for the oxidation of quinol to quinone, while potentiometrically the first two give two discrete one-electron redox steps, indicating the formation of a stable semiquinone; there appears to be no simple relation between polarographic $E_{\frac{1}{2}}$ values and potentiometric standard redox potentials. Since most, if not all, of the dyes in Table 1 give a single wave for the polarographic oxidation of the quinol, despite considerable variation in fading and tendering activity, it is clear that polarography is incapable of revealing whether such activity is related to semiquinone formation.

When the dyes examined are placed in order of increasing $E_{\frac{1}{2}}$ for the quinol oxidation step, it appears that, despite some variation in the order with change of pH, there is some correlation with light-fastness, which decreases as $E_{\frac{1}{2}}$ becomes more negative. No such correlation of $E_{\frac{1}{2}}$ with tendering activity is apparent.

MEDWAY COLLEGE OF TECHNOLOGY, CHATHAM, KENT. [*Received, December 8th*, 1957.]

[24] Bradley and Maisey, *J.*, 1954, 274.

680. *Fading and Tendering Activity in Anthraquinonoid Vat Dyes. Part V.*[1] *Photo-dehalogenation and -oxidation of* leuco-*Solutions.*

By C. J. Cooper and H. I. Stonehill.

leuco-Solutions of the halogenated dyes Cibanone Brilliant Orange GK and Gold Yellow RK, and Caledon Brilliant Orange 6R, Orange 2RTS, and Brilliant Orange 4RN undergo rapid dehalogenation when exposed to visible light. In the presence of excess of dithionite dehalogenation is complete, but in catalytically prepared *leuco*-solutions with no excess of reductant dehalogenation proceeds to the extent of statistically one halogen atom per molecule, which releases sufficient oxidant to oxidise completely and thus precipitate all the *leuco*-dye present. Thus a dye containing n halogen atoms per molecule can undergo n successive reduction–irradiation–precipitation cycles. Potentiometric determinations show that not all the halogen liberated appears as halide ion; some is probably lost by adsorption on precipitated dye. Examination of the irradiation products by chromatography, *X*-ray diffraction, and conventional and differential absorption spectroscopy confirms the dehalogenation, and indicates that no monohalogenated product is formed from either di- or tri-halogenated dyes. The occasional production, under severe reducing conditions, of a *leuco*-solution which was not rapidly precipitated on irradiation, an effect enhanced by pyridine, is ascribed to the formation of tautomeric oxanthranol. The visible and ultraviolet absorption spectra of the catalytically prepared *leuco*-solutions of the above five dyes and nine others were determined, and by irradiation in the spectrophotometer the spectral region responsible for photo-dehalogenation was located as approximately 450—650 mμ for all five dyes concerned.

During preliminary work on the polarographic oxidation of *leuco*-Caledon Orange 2RTS,[1] difficulty was experienced in obtaining reproducible wave-heights. Since neither a rise in temperature from 25° to 50°, nor replacement of 48% aqueous ethanol as solvent by 50% aqueous pyridine, as used by Appleton and Geake [2] for potentiometric titrations, decreased the variability, the latter was not caused by precipitation of *leuco*-dye on cooling from the reduction temperature to 25°. It was traced to the action of light on the *leuco*-solution. When a thin layer of the purple *leuco*-solution in the capillary tube connecting the reduction vessel and the polarographic cell was illuminated by a 60-watt lamp a few inches from it, the liquid became colourless within a few minutes and a yellow precipitate appeared. In the dark, no fading or precipitation occurred after 1 hr., and polarographic wave-heights were reproducible and proportional to concentration. Hence subsequent polarograms were obtained in the dark.

Since precipitation was observed only if the *leuco*-solution was illuminated after removal from contact with the reduction catalyst, it was apparently due to oxidation, which would occur only in the absence of a reductant. Accordingly, the following rapid test was used to select those dyes among the 39 listed by Moran and Stonehill [3] which behaved like Caledon Orange 2RTS. An aqueous suspension of the dye was reduced with the minimum quantity of alkaline sodium dithionite solution, and equal volumes of the resulting *leuco*-solution were placed in two test-tubes. The surface of each solution was quickly covered with liquid paraffin to exclude air, and 1 ml. of 40% aqueous formaldehyde was added by means of a pipette below the oil layer, destroying excess of dithionite. One tube was immediately placed in a dark cupboard, and the other illuminated with a 100-watt electric lamp a few inches away. The extent of dye precipitation in the tubes was periodically

[1] Part IV, Cooper and Stonehill, preceding paper.
[2] Appleton and Geake, *Trans. Faraday Soc.*, 1941, **37**, 45, 60.
[3] Moran and Stonehill, *J.*, 1957, 765.

compared. The test was not completely reliable, especially for detecting slight photo-oxidation, since the crude method of excluding air permitted slight atmospheric oxidation. However, it showed clearly that only the five dyes named in the summary were strongly active, and examination under rigorous anaerobic conditions of catalytically prepared *leuco*-solutions [1] confirmed that these dyes alone underwent photoprecipitation.

All five active dyes are halogenated. The reported lability of halogen atoms, in certain vat dyes, to high vatting temperatures [4] and sunlight [5] suggests dehalogenation as a likely explanation of the photo-oxidation activity. Bradley [6] found that alkali replaced the halogen of dibromoanthanthrones by hydroxyl. This would not, however, provide oxidant which is necessary to account for the photo-oxidation and precipitation in the *leuco*-solutions. The replacement of halogen by hydrogen, on the other hand, provides the necessary oxidant, as shown by the purely stoicheiometric reaction

$$X_nR(O^-)_2 + H_2O \longrightarrow X_{(n-1)}HRO_2 + X^- + OH^- \quad (X = \text{halogen}) \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Photo-induced exchange of halogen for hydrogen was reported by Goldstein and Gardner [7] for monohalogenated anthraquinols in visible light; they found α- more labile than β-halogen, and bromine more so than chlorine. In the highly alkaline *leuco*-solutions concerned here, the hydrogen substituent cannot be provided by hydrogen ions, and must presumably come from water molecules, as in reaction (1). Since replacement of only one halogen atom per molecule by hydrogen is sufficient to oxidise the *leuco*-dye completely, a dye with n halogen atoms per molecule should be photoactive for n successive cycles of reduction and exhaustive irradiation. This was verified for dyes with $n = 2$ and 3. No further activity was found after n cycles.

In order to obtain direct evidence of photo-dehalogenation, and to determine the amount of halide ion formed after each exhaustive irradiation, use was made of halide-ion concentration cells. The identity of the irradiation products was studied by comparing their absorption spectra and *X*-ray diffraction patterns with those of the original dyes and their unhalogenated analogues, and by using chromatographic separations and differential absorption spectroscopy. In connection with the spectrophotometric identification of the spectral region responsible for photo-dehalogenation of the *leuco*-dyes, the visible absorption spectra of their solutions were determined. The opportunity was taken to determine also their ultraviolet absorption spectra. To avoid errors due to ultraviolet absorption by the excess of dithionite used for reduction in previous work on the *leuco*-spectra,[3] the *leuco*-solutions were prepared by catalytic reduction.

Experimental

Materials.—Dioxan (technical) was refluxed with concentrated hydrochloric acid, and distilled over sodium. Phenol was of " AnalaR " grade. Other materials were as described previously.[1,3]

Preparation of Irradiation Products.—A quantity of halogenated dye, sufficient to give 50 ml. of approx. mM-*leuco*-solution, was catalytically reduced as previously described [1] for polarography, and passed into the polarographic cell from which the electrodes had been removed. It was irradiated by a 100-watt electric lamp a few inches away, and samples of the well-shaken resulting suspension were removed after precipitation was complete (usually within 5 min.). An attempt to prepare the product of two or more successive reduction–irradiation cycles without removing the dye sample from the apparatus or renewing the catalyst failed because of poisoning of the catalyst by traces of *leuco*-solution on it which underwent photo-dehalogenation–oxidation during irradiation. Palladised and platinised asbestos catalysts were far more severely poisoned than Raney nickel.

Determination of Bromide Ion Formed on Irradiation.—A 5 ml. portion of irradiated *leuco*-solution was filtered, after atmospheric oxidation if necessary to complete precipitation, and

[4] Fox, *J. Soc. Dyers and Colourists*, 1949, **65**, 508.
[5] Weber, *Amer. Dyestuff Reporter*, 1933, **22**, 157.
[6] Bradley, *J. Soc. Dyers and Colourists*, 1954, **70**, 57.
[7] Goldstein and Gardner, *J. Amer. Chem. Soc.*, 1934, **56**, 2131.

combined with a reference potassium bromide solution (mM or 0·5mM) to form the concentration cell:

$$Ag \mid AgBr\ (s),\ test\ soln.,\ [Br^-] = c_1 \parallel reference\ soln.,\ [Br^-] = c_2,\ AgBr\ (s) \mid Ag$$

The E.M.F. (E mv) of this cell was measured at 25° with a Cambridge pH meter used as a valve potentiometer, and the value of c_1 calculated from the equation $E = 59 \log c_1/c_2$. The electrodes were silver-wire spirals coated electrolytically with silver bromide. They dipped into small beakers containing the appropriate solutions and connected by a salt-bridge tube fitted with ground-glass end-stoppers. To minimise junction potentials, test, bridge, and reference solutions contained the same high concentration of indifferent electrolyte as carrier solution. Since the *leuco*-solutions contained 0·1N-sodium hydroxide and 48% ethanol, this was at first tried as carrier solution. However, it caused drifting potentials in cells with known potassium bromide concentrations for both electrode solutions, probably owing to the effect of alkali on the electrodes. Erratic behaviour persisted in these cells on neutralisation of the solutions with 2N-nitric acid from a micro-burette (to Methyl Orange), but disappeared on addition to the neutralised solutions of a little solid sodium hydrogen carbonate as buffering agent. The test cell then gave reproducible non-drifting E values in accordance with the above equation. All cell solutions were thereafter treated similarly.

Absorption Spectra.—The precipitated irradiation product of each active *leuco*-solution was extracted from its suspension in alkaline aqueous ethanol with warm chlorobenzene, the extract dried (CaO) and filtered into an absorption cell (usually of 4 cm. optical path), and its visible absorption spectrum determined with the Hilger Uvispek spectrophotometer, fitted with a glass prism. Concentration was not controlled. Comparison spectra of chlorobenzene solutions of the original halogenated dyes and of their unhalogenated analogues were also determined.

leuco-Solution spectra were determined in both the ultraviolet and the visible region with the Uvispek instrument, solutions being prepared in the dark as follows. A suitable quantity of standard dye suspension in 50% v/v aqueous ethanol containing 0·1N-sodium hydroxide was reduced at 55° for ½ hr. with hydrogen and palladium or partially deactivated Raney nickel in the apparatus previously described.[1] One batch of palladium catalyst caused dehalogenation during reduction, and was rejected; nickel catalyst which had not been deactivated caused dehalogenation and produced fluorescent solutions. Interposed between the reduction vessel and the polarographic cell was a 2 cm. quartz absorption cell, fitted with a latex-gasketed airtight cap bearing integral inlet and outlet tubes and fabricated from a single block of Perspex; these tubes were connected to the rest of the apparatus by short lengths of polyvinyl chloride tubing bearing screw clips. The solution was diluted in the apparatus with sufficient aqueous 0·1N-sodium hydroxide to reduce the ethanol concentration to 16% v/v, cooled, and filtered through glass wool into the absorption cell. When this was completely filled, the screw clips were closed, and the cell was detached from the assembly and, while still shielded from light, placed in the spectrophotometer. Despite the photo-activity of the *leuco*-solutions of halogenated dyes, the extent of photo-reaction during the determination of absorption spectra was found to be negligible with the low-powered 8-watt filament lamp light source of the Uvispek instrument, provided the maker's recommended slit widths for a 5 Å band-width were used with minimal exposure of the solutions. With a solution of the same composition, apart from omission of dye, as reference, the absorption spectra frequently exhibited a sharp maximum near 235 mμ, the intensity of which varied with the duration and temperature of reduction but was practically independent of dye or ethanol concentration, the nature of the alkali used, and the presence or absence of hydrogen or air in the reference solution. This may be either a spurious maximum [8] due to strong absorption by ethanol and sodium hydroxide in this spectral region, or else the absorption band of material extracted from the polyvinyl chloride tubing by the aqueous ethanol; the material extracted with 90% aqueous methanol has an absorption band at 225 mμ.[9] By using as reference solution a sample of the *leuco*-solution which was air-oxidised and filtered through glass wool after any colloidal dye had coagulated (15 min.), the optical density of this maximum was reduced to about 0·3; with the high concentrations of dye used, its effect on the position of dye absorption maxima in the 240 mμ region is probably small.

Identification of Spectral Region causing Photo-dehalogenation.—Each active *leuco*-solution,

[8] Bayliss and Brackenbridge, *Chem. and Ind.*, 1955, 477.
[9] Banks, Fazakerley, Keay, and Smith, *ibid.*, 1957, 1013.

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prepared as described above, was irradiated for ½ hr. in the Uvispek apparatus with light from a 36-watt filament lamp source in a 25 Å band (obtained by widening the instrument slit width) centred on each in turn of the visible absorption maxima, and the optical density was measured before and after each irradiation. When a decrease in optical density occurred, the contents of the absorption cell were mixed by shaking before further irradiation. The active spectral region having thus been approximately located, further ½ hr. irradiations were performed with 25 Å band widths in neighbouring spectral regions to determine the limits of the active region; these were confirmed with fresh *leuco*-solution. Spectral regions causing no decrease in optical density after ½ hour's exposure were still without effect after exposure for 2 hr.

X-*Ray Diffraction Powder Photographs.*—Samples of Caledon Brilliant Orange 6R, its final product after two reduction–irradiation cycles, and its unbrominated analogue anthanthrone were recrystallised from chlorobenzene, and their *X*-ray powder diffraction photographs obtained by means of a Phillips *X*-ray diffraction apparatus, type 11704, fitted with a 11·46 cm. Debye–Scherrer powder camera.

Chromatographic Procedures.—Ascending filter-paper chromatograms of the irradiation products of active *leuco*-dyes, and of reference dyes and mixtures thereof, were obtained by impregnating one end of 12 in. × 1 in. paper strips with the appropriate dithionite-reduced *leuco*-solution, allowing air-oxidation to occur, washing out inorganic materials with water, drying, and suspending the paper overnight in gas jars with the impregnated lower end dipping into chlorobenzene. The constituents of the first irradiation product of the active dibrominated dye Caledon Brilliant Orange 6R were separated by column chromatography; a solution in chlorobenzene was poured on a 24 in. × 1 in. alumina column and developed with chlorobenzene until the yellow band was separated from the immobile narrow orange band; portions of the latter zone and each end of the extended yellow band were extracted with chlorobenzene, and the visible absorption spectra of the extracts plotted.

Results and Discussion

(i) *Bromide Ion Liberated on Irradiation of* leuco-*Solutions.*—Caledon Brilliant Orange 6R, a dibromo-dye, was reduced at 80° for 1 hr. in 48% v/v aqueous ethanol containing 0·1N-sodium hydroxide. The bromide ion liberated after various numbers of reduction–irradiation cycles is given in Table 1. To establish whether this release of bromine

Table 1.

Dye concn. (mM)	0·42	0·862	0·862	0·862	0·862
No. of cycles	4	1	3	1	3
Br^- liberated (ions/dye mol.)	1·05	0·75	1·40	0·40	0·96

occurs on irradiation or merely on reduction, the bromide concentration was determined in a portion of 0·862mM-*leuco*-solution after air-oxidation in the dark. The result, approximately 0·02 Br^- ion per dye molecule, indicates that virtually no dehalogenation of dye occurs in the absence of irradiation.

The amount of bromide ion released in these experiments is much less than that according to reaction (1), namely, one ion per dye molecule for each of the first two irradiations. Similar low yields of bromide (see Table 2) were obtained with 0·774mM-

Table 2.

Run	A			B			C	
No. of irradiations	1	2	3	1	2	1	2	3
Br^- liberated (ions/dye mol.)	0·22	0·48	0·62	0·16	0·29	0·11	0·16	0·26

Table 3.

Solvent	48% pyridine		48% pyridine		48% dioxan		48% EtOH + 0·01M-PhOH
No. of irradiations	1	2	1	3	1	3	1
Br^- liberated (ions/dye mol.)	0·96	1·65	0·85	1·23	0·82	1·36	0·76

leuco-solutions of Caledon Brilliant Orange 4RN, the only trihalogenated dye available, prepared in the same way. This suggests that some of the bromide ion is removed from

solution by entrainment in, or adsorption on, the precipitated quinones. The limited data available are in fact consistent with a Freundlich-type adsorption isotherm.

The alternative possibility, suggested by the ester-like odour of irradiated solutions, that some of the liberated bromine atoms were removed by reaction with the ethanol to become covalently bound, is not only energetically improbable,[10] but is not supported by the results obtained (Table 3) on irradiating 0·862mM-*leuco*-Caledon Brilliant Orange 6R in 48% aqueous pyridine or dioxan, which are brominated less readily than ethanol, and in 48% aqueous ethanol containing phenol, which reacts readily with bromine atoms. In fact, bromide recovery is not significantly different with the various solvents used, and may approach the theoretical value for the first irradiation quite closely. Precipitation during irradiation was noticeably slower in pyridine than in ethanol, and on completion left a slightly coloured supernatant solution, whereas with ethanol the latter was colourless (cf. section iv). When the precipitate from an irradiated pyridine solution was filtered off and the filter-paper allowed to dry in air, the paper had an odour suggesting the presence of acetamide; this might indicate some attack on the pyridine, since it was not observed unless the photo-reaction had occurred.

(ii) *Identification of Final Irradiation Products.*—The absorption spectra of chlorobenzene solutions of various active halogenated dyes, their successive reduction–irradiation products, and the corresponding inactive unhalogenated dyes were determined in the visible region. Absorption peak wavelengths are given in Table 4, and a complete set

TABLE 4. *Absorption maxima for active dyes, their irradiation products, and their unhalogenated analogues.*

Dye	No. of halogen atoms in mol.	No. of irradiations	$\lambda_{max.}$ (mμ)		
Caledon Brilliant Orange 6R	2	0	492	462	—
		1	484	456	—
		2	478	450	—
Cibanone Brilliant Orange GK	2	0	492	465	—
		1	484	458	—
		2	478	450	—
Anthanthrone	0	0	478	450	—
Caledon Orange 2RTS	2	0	488	456	435
		1	482	450	431 *
		2	474	443	424 *
Caledon Brilliant Orange 4RN	3	0	496	465	435
		1	491	461	435
		2	483	450	430 *
		3	474	444	423 *
Caledon Gold Orange G	0	0	474	443	424 *
Cibanone Golden Yellow RK	2	0	473	443	420
		1	469	440	415
		2	466	436	410
Cibanone Golden Yellow GK	0	0	466	436	410

* Inflection.

of spectra for the representative dye Caledon Brilliant Orange 4RN in Fig. 1. The absorption maxima of successive irradiation products show a progressive bathochromic shift until, after as many irradiations as there are halogen atoms in the dye molecule, they coincide with those of the analogous unhalogenated dyes.

Confirmation of the identity of the final irradiation product of Caledon Brilliant Orange 6R and the unhalogenated analogue anthanthrone was obtained from a comparison of their *X*-ray powder diffraction patterns.

(iii) *Identification of Intermediate Irradiation Products.*—Reaction (1) requires the loss of statistically one halogen (X) atom per dye molecule. For a dihalogenated dye, this

[10] Walling, "Free Radicals in Solution," John Wiley & Sons, Inc., New York, 1957, p. 370.

could occur either by all the dye molecules losing one, or half the dye molecules losing both halogen atoms:

$$X_2R(O^-)_2 + H_2O \longrightarrow X^- + OH^- + XHRO_2 \quad . . . . . (3)$$

$$2X_2R(O^-)_2 + 2H_2O \longrightarrow 2X^- + 2OH^- + X_2RO_2 + H_2RO_2 \quad . . . . . (4)$$

Since the absorption peaks are broadened for the intermediate irradiation products (Fig. 1), the latter would appear to be mixtures. To decide this, paper-strip ascending chromatograms were obtained for (*a*) Caledon Brilliant Orange 6R, (*b*) its first reduction–irradiation product, (*c*) the unhalogenated analogue anthanthrone, and (*d*) an equimolar mixture of (*a*) and (*c*). For (*a*), a narrow undevelopable orange band was obtained; for (*c*), a broad developable yellow band; for both (*b*) and (*d*), both these bands. A larger quantity of (*b*) was separated chromatographically on an alumina column: the orange and the yellow fraction gave absorption spectra identical respectively with those of (*a*) and (*c*). Thus the first photo-dehalogenation proceeds, as regards the products, according to reaction (4),

FIG. 1. *Spectra of* (*a*) *Caledon Brilliant Orange* 4*RN, and its* (*b*) *first,* (*c*) *second, and* (*d*) *third irradiation product, in* PhCl (4 *cm. cell*).

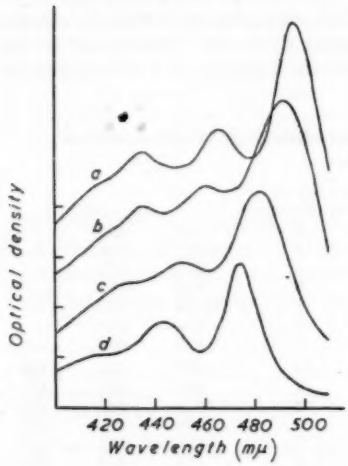
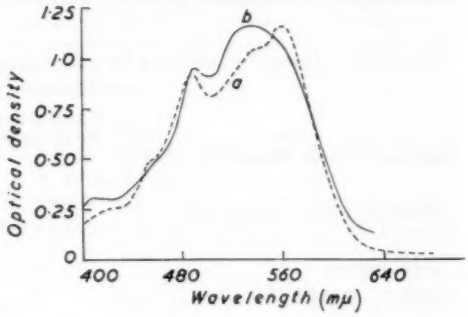


FIG. 2. *Absorption spectrum of* leuco*anthanthrone reduced at* (*a*) 55° *for* ½ *hr. and* (*b*) 85° *for* 4 *hr., with hydrogen and palladium, in* 48% *aq.* EtOH + 0·1N-NaOH (2 *cm. cell length*).



and there is no evidence of the formation of the monohalogenated dye. It is nevertheless more plausible to suppose (cf. section viii), that the initial dehalogenation product is the monohalogenated semiquinone or quinol. Some of this may be further dehalogenated and then oxidised to unhalogenated quinone, while the greater part must be assumed to undergo disproportionation to dihalogenated and unhalogenated analogues, either in solution as quinol or semiquinone, or after precipitation as quinone, probably upon redissolution, *e.g.*, in chlorobenzene for spectral examination. The original quinone precipitate might then consist of mixed crystals of molecules containing 0, 1, and 2 halogen atoms. In this connection it is of interest that the first irradiation product of Caledon Brilliant Orange 6R gave an *X*-ray powder diffraction pattern different from that of an equimolar mixture of the original dye and anthanthrone, the difference being largely removed by recrystallisation of the product from chlorobenzene.

Further examination of the first irradiation product of dihalogenated dyes was made by differential absorption spectroscopy. The visible absorption spectrum in chlorobenzene was determined with a chlorobenzene solution of the original dye in the reference cell, the concentration of the latter solution being adjusted to match that of the original dye in the test solution by diluting with solvent until the optical densities balanced at a wavelength

at which the original dye, but not its unhalogenated analogue, absorbs appreciably; this is possible because the halogenated dyes absorb at longer wavelengths than their unhalogenated analogues. The resulting differential absorption spectrum should be due entirely to solutes present other than the original dye. The technique was capable of indicating in 1 : 4 to 4 : 1 synthetic mixtures of halogenated and unhalogenated dyes both the presence and the approximate concentration ratio of the latter constituents. For the first irradiation products of Caledon Brilliant Orange 6R, Caledon Brilliant Orange GK, Caledon Orange 2RTS, and Cibanone Golden Yellow RK, the absorption peak wavelengths of the differential spectra corresponded with those of the unhalogenated analogues, and the optical density corresponded to approximately equimolar amounts of the original dye and its unhalogenated analogue.

For the tribrominated dye Caledon Brilliant Orange 4RN we may suppose, by analogy, that the initial product of the first irradiation is a mixture of the semiquinones and quinols with 0—3 bromine atoms per molecule. Again the monobromo-quinol, -semiquinone, and -quinone must be presumed to undergo bromine disproportionation, so that eventually only the original dye, the dibromo-dye (Caledon Orange 2RTS), and the unbrominated analogue (Caledon Gold Orange G) are present. The differential absorption spectrum of the first irradiation product of the tribromo-dye (the original dye being used as reference) has peaks at 485, 454, and 433 mμ. Comparison with the peak wavelengths for the first irradiation product of Caledon Orange 2RTS (Table 4) suggests the presence of the latter dye together with rather less than an equimolar amount of Caledon Gold Orange G. The quantities of the tribromo-, dibromo-, and unbrominated dyes are finally estimated from peak intensities to be approximately in the molar ratios 4 : 3 : 2. This satisfies the stoicheiometric requirement of statistical loss of one bromine atom per dye molecule, as in either of the processes

$$3Br_3R(O^-)_2 + H_2O \longrightarrow H_3RO_3 + 2Br_3RO_2 + 3Br^- + 3OH^-$$
$$Br_3R(O^-)_2 + H_2O \longrightarrow Br_2HRO_3 + Br^- + OH^-$$

both of which, as regards the final products, must be assumed to occur.

(iv) *Oxanthranol Formation.*—The residual purple solution left after irradiating the *leuco*-solution of Caledon Brilliant Orange 6R in 48% aqueous pyridine was mentioned in section (i). With aqueous ethanol as solvent, this purple colour was only occasionally obtained. Whereas irradiation normally caused complete precipitation within 5 min., leaving a colourless liquid, the purple colour, when it occurred, persisted for up to 2 hr. under irradiation, fading gradually. Since certain anthraquinonoid *leuco*-dyes tautomerise to oxanthranols, especially when incompletely ionised,[11] $R(OH)_2 \rightleftharpoons O{:}RH{\cdot}OH$, it was of interest to find whether the occurrence of the purple solution and the failure to undergo rapid and complete precipitation in light were due to the formation during reduction of some oxanthranol, which slowly reverts to the quinol as the latter is removed during irradiation.

Since oxanthranol formation is enhanced by severe vatting conditions,[11] a preliminary investigation was made of the effect of varying the duration and temperature of vatting on the visible absorption spectrum of the *leuco*-solution obtained by catalytic reduction (palladised asbestos) in 48% aqueous ethanol containing 0·1N-sodium hydroxide, the unhalogenated dye anthanthrone being used in order to avoid complications from dehalogenation during vatting. The spectra obtained after vatting at (*a*) 55° for ½ hr. and (*b*) 85° for 4 hr. are shown in Fig. 2. Clearly, the severe conditions of (*b*) cause modifications of the spectrum, which may be due to enhanced oxanthranol formation.

Next, a 0·862mM-*leuco*-solution of Caledon Brilliant Orange 6R in the same solvent was prepared similarly under fairly severe conditions (1 hr. at 65—70°), cooled, irradiated for ½ hr. so that the supernatant liquid was only faintly purple, and filtered. Its visible absorption spectrum differed very greatly from that of the original *leuco*-solution. The filtered solution was then irradiated for a further 3 hr., a yellow precipitate being

[11] Coffey, *Chem. and Ind.*, 1953, 1068.

formed and the solution becoming colourless. The precipitate, which underwent no visible change on exposure to air, was extracted with chlorobenzene. Its visible absorption spectrum in this solvent was found to be identical with that of anthanthrone. This accords with the view that half of the solute in the purple solution was the dibromo-oxanthranol derived from the original dye, the other half being the oxanthranol, or less probably the quinol, derived from anthanthrone. Thus there is strong evidence of the formation of oxanthranol on vigorous vatting.

(v) leuco-*Dye Spectra.*—Wavelengths and molar extinction coefficients of absorption peaks in both the visible and the ultraviolet region are given in Table 5, although only the visible spectra were required in connection with the identification of the spectral regions causing photo-dehalogenation. Agreement with the earlier determinations of the visible spectra by Moran and Stonehill [1] is satisfactory, apart from a few minor discrepancies probably due to less effective prevention of atmospheric reoxidation in the earlier work.

(vi) *Absorption Bands causing Photo-dehalogenation.*—The upper and lower wavelength limits of the active bands and their means are listed in Table 6. The technique used is incapable without further refinement of determining the wavelengths for maximum activity, but it is significant that for each *leuco*-dye the mean of the extreme wavelengths corresponds approximately with a main absorption peak listed in Table 5. No activity was detected in the ultraviolet range available with the spectrophotometer.

TABLE 5. *Ultraviolet and visible absorption spectra of* leuco-*dyes.*

Results are for $c \times 10^{-5}$M-solutions in 16% aqueous ethanol containing 0·1N-sodium hydroxide, in 2 cm. cells. Italics indicate an inflection.

Dye	c	$\lambda_{max.}$ (mμ)/log ε
Algol Yellow WG	4·0	234/3·96, 279/4·25, *302/4·08*, *405/3·84*, 423/4·00, 535/3·79
Caledon Red X5BS	5·0	243/4·11, 286/4·19, *300/4·13*, *335/3·81*, *417/3·68*, 436/3·79, 558/3·72
Caledon Red 5G	4·0	234/4·13, 275/4·29, 327/3·83, *343/3·76*, *394/3·70*, 411/3·81, 431/3·76, 494/3·70, 560/3·49
Anthanthrone	5·0	243/4·22, 256/4·23, 316/4·26, *430/3·34*, *458/3·66*, 487/3·98, 535/4·03, 559/4·06
Cibanone Brilliant Orange GK	4·0	239/4·37, 261/4·35, 324/4·33, *465/3·72*, 493/3·96, *560/3·99*, 580/4·02
Caledon Brilliant Orange 6R	3·5	244/4·31, 261/4·32, 325/4·30, *464/3·69*, 493/3·93, *559/3·98*, 582/4·02
Caledon Gold Orange G	5·0	238/3·91, 256/3·92, 295/4·09, 308/4·10, *330/3·59*, *345/3·42*, 390/3·15, *515/3·97*, 545/4·06
Caledon Orange 2RTS	7·5	243/3·91, 264/3·93, 301/4·12, 311/4·08, *350/3·40*, 390/3·11, *525/3·98*, 554/4·05
Caledon Brilliant Orange 4RN	6·5	246/3·81, 265/3·85, 307/4·07, *350/3·32*, 390/3·11, *530/3·96*, 559/4·03
Cibanone Golden Yellow GK	3·5	235/4·10, 272/4·00, *304/4·12*, 313/4·21, *456/3·82*, 479/3·97, 516/3·72, 554/3·69
Cibanone Golden Yellow RK	6·0	244/4·10, 276/4·09, 321/4·24, *464/3·86*, 488/4·05, *525/3·72*, 560/3·65
Cibanone Blue RSN	2·0	240/4·22, 300/4·32, 320/4·38, *360/3·72*, 550/3·60, 730/3·95
Caledon Blue RC	3·0	242/4·15, *304/4·25*, 323/4·46, *370/3·72*, 565/3·52, 770/4·15

(vii) *Photo-dehalogenation in the Presence of Excess of Reductant.*—Dilute suspensions of the photo-active dyes were reduced with excess sodium dithionite in 0·1N-aqueous sodium hydroxide, and the *leuco*-solutions were illuminated by a 100-watt electric lamp at a few inches distance for ½ hr. Comparison with control solutions kept in the dark showed that irradiation caused a change of colour towards that of the corresponding unhalogenated *leuco*-dye solution. Both the controls and the irradiated solutions were then air-oxidised, and the visible absorption spectra of the precipitates were determined after extraction into chlorobenzene. In all cases the spectrum of the control coincided with that of the original dye, while that of the irradiated sample corresponded with that of the unhalogenated analogue, indicating complete dehalogenation.

(viii) *Mechanism of Photo-dehalogenation of* leuco-*Solutions.*—The above work leads to the following conclusions: (*a*) The rapidity of photo-dehalogenation implies that the

dye quinol rather than the semiquinone is the species primarily attacked, since the semiquinone is present to only a very small extent, especially in the presence of excess of reductant. (*b*) Photo-oxidation of *leuco*-dye, which accompanies the dehalogenation if the reductant is not in excess, requires transfer of electrons from the dye to a reducible

TABLE 6. *Waveband responsible photo-dehalogenation.*

Dye	Active wavelengths (mμ) Lower limit	Upper limit	Mean
Cibanone Brilliant Orange GK	460	650	555
Caledon Brilliant Orange 6R	460	650	555
Caledon Orange 2RTS	480	630	555
Caledon Brilliant Orange 4RN	450	670	560
Cibanone Golden Yellow RK	480	620	550

species; of those available, water is more probably involved than hydrogen ion in view of the high pH, especially in the hydration shell surrounding the dye molecule. (*c*) The halogen is liberated as free atoms, since a tribromo-dye yields some dibromo-dye on photo-dehalogenation. (*d*) Statistically one halogen atom per dye molecule is lost in a single exhaustive irradiation, but recovery of halide ion in solution may be less than corresponds to this because of adsorption on or entrainment with precipitated quinones. (*e*) Upon photo-dehalogenation a dihalogenated dye gives products with 0 and 2 halogen atoms per molecule, a trihalogenated dye products with 0, 2, and 3 halogen atoms per molecule; neither gives a monohalogenated product.

On the basis of conclusions (*a*)—(*d*), a mechanism for photo-oxidation–dehalogenation was proposed by Moran and Stonehill.[12] This requires some modifications in view of (*e*). It is now suggested that monohalogenated quinols and semiquinones are formed as intermediates, but are further dehalogenated by H· radicals or undergo disproportionation to dihalogenated and unhalogenated analogues in solution or after oxidation to quinones, especially when the latter are dissolved for recrystallisation or spectral examination. The modified reaction scheme is as follows, it being assumed that no excess of reductant is present, and $m = 2$ or 3.

$$X_mR(O^-)_2 + h\nu \longrightarrow X_mR(O^-)_2{}^* \text{ (singlet excited state)} \quad (5)$$

$$X_mR(O^-)_2{}^* \longrightarrow X_mR(O^-)_2{}^{**} \text{ (triplet excited state)} \quad (6)$$

$$X_mR(O^-)_2{}^{**} + H_2O \longrightarrow X_mRO^-O^\cdot \text{ (semiquinone)} + H^\cdot + OH^- \quad (7)$$

The H atom released per quinol molecule photo-oxidised to semiquinone displaces an equivalent of halogen atoms from any halogenated quinol or semiquinone, usually only one from any molecule, but occasionally 2 or, when possible, 3:

$$X_mRO^-O^\cdot \text{ (or corresponding quinol)} + H^\cdot \longrightarrow HX_{(m-1)}RO^-O^\cdot \text{ (or corresponding quinol)} + X^\cdot \quad (8)$$

Some $H_2X_{(m-2)}RO^-O^\cdot$, $H_mRO^-O^\cdot$, and the corresponding quinols are produced by repetition of process (8). When all the quinols have been completely photo-oxidised to semiquinones, the halogen atoms released are sufficient to oxidise all semiquinones to quinones:

$$H_nX_{(m-n)}RO^-O^\cdot + X^\cdot \longrightarrow H_nX_{(m-n)}RO_2 + X^- \ (m \geqslant n \geqslant 0)$$

Disproportionation of any monohalogenated quinol, semiquinone, or quinone removes any monohalogenated quinol from the final product: $2H_{m-1}XR(O^-)_2$ (or corresponding semiquinone or quinone) $\longrightarrow M_mR(O^-)_2 + H_{(m-2)}X_2R(O^-)_2$ (or corresponding semiquinones or quinones).

In the presence of excess of reductant, *e.g.*, dithionite, reactions (5—8) are followed by reduction of X· to X^- and of the semiquinones to quinols, which may then undergo the same reaction sequence until dehalogenation is complete.

We thank Mr. F. L. Grace, M.A., M.Sc., for the *X*-ray photographs.

MEDWAY COLLEGE OF TECHNOLOGY, CHATHAM, KENT. [*Received, December 9th*, 1957.]

[12] Moran and Stonehill, *J.*, 1957, 788.

681. *Fading and Tendering Activity in Anthraquinonoid Vat Dyes. Part VI.* The Coulometry of the Polarographic Oxidation of* leuco-*Dyes.*

By C. J. Cooper and H. I. Stonehill.

The number of electrons per molecule involved in the polarographic oxidation of *leuco*-solutions of 12 anthraquinonoid vat dyes and one related quinone was determined micropolarographically. It is 2 for all the compounds except those five which are halogenated and undergo photo-dehalogenation–oxidation in *leuco*-solution; for these, the apparent number of electrons is one. By conventional and differential absorption spectroscopy the products of the exhaustive polarographic oxidation of the dihalogenated photo-active *leuco*-dyes are shown to contain about 25 moles % of the analogous unhalogenated dye. Both this partial dehalogenation and the low electron loss during electro-oxidation are accounted for by a tentative reaction scheme in which a *leuco*-dye molecule adsorbed on the mercury-drop anode is dehalogenated by the joint action of mercury and water, either during or after electro-oxidation, yielding mercury halide and a hydroxyl radical, which then oxidise another *leuco*-dye molecule.

In order to interpret the oxidative polarograms of the *leuco*-dyes described in Part IV,[1] a knowledge was required of the number (n) of electrons per molecule involved in the oxidations. Logarithmic analysis was inapplicable since the polarographic waves are irreversible. For the benzamidoanthraquinols, the insertion in the Ilković equation [2] of a diffusion coefficient equal to the average value for some substituted anthraquinols, estimated from Gill and Stonehill's polarographic data,[3] led to indeterminate n values. Accordingly, Gilbert and Rideal's micropolarographic method [4] was used to provide essentially coulometric n values under electrolysis conditions virtually identical with those of macropolarography. In this method, a small volume (v litres; *ca.* 0·25 ml.) of solution, of concentration c mole/l., is electrolysed at the dropping-mercury electrode at a potential corresponding to a point on the diffusion-current plateau. The gradually decreasing wave-height i is measured periodically, and, from the slope of the linear graph of log i against t (duration of electrolysis in sec.), n is calculated by means of the equation

$$n = -i_0/2{\cdot}303\ cv\mathbf{F}\ (\mathrm{d}\log i/\mathrm{d}t)$$

where i_0 is the value of i for $t = 0$.

To investigate the extent of dehalogenation during the electrolysis of halogenated *leuco*-dyes, the products of exhaustive electrolysis were examined by conventional and differential absorption spectroscopy.

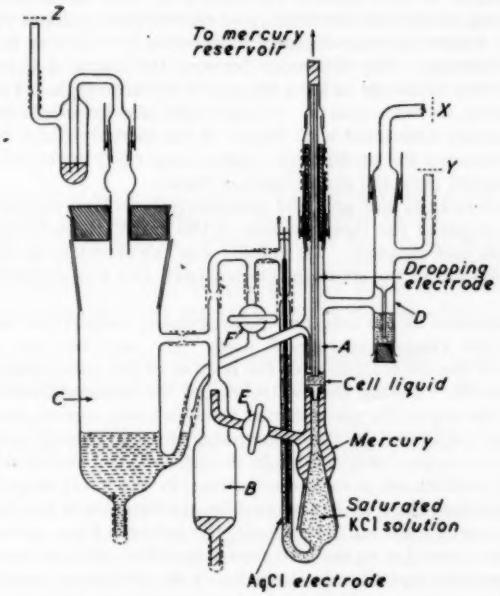
Experimental

Apparatus and Materials.—A micropolarographic cell was designed to permit about 10^{-7} mole of *leuco*-dye, completely oxidisable by only 0·006 ml. of air, to be protected from atmospheric oxidation for several hours. The cell (see Figure) was connected at X, Y, and Z to the correspondingly lettered parts of the dye-reduction apparatus described previously.[1] The broken lines represent connections or caps made of poly(viny chloride) tubing. The solution undergoing electrolysis in tube A, in contact with the minimum volume of gas, floated on a column of mercury kept at constant level, despite influx of mercury from the dropping electrode, by overflow through tap E into vessel B. A U-tube, one end of which projected just above the

* Part V, preceding paper.

[1] Cooper and Stonehill, *J.*, 1958, 3341.
[2] Ilkovic, *Coll. Czech. Chem. Comm.*, 1934, **6**, 498.
[3] Gill and Stonehill, *J.*, 1952, 1845.
[4] Gilbert and Rideal, *Trans. Faraday Soc.*, 1951, **47**, 396.

mercury level in *A*, where it was closed with a small ground-glass stopper, was filled to the stopper with saturated aqueous potassium chloride solution. Into this dipped, in the other limb of the U-tube, an external cathode of silver wire coated anodically with silver chloride and welded to a platinum wire fused through the sealed end of the limb. Tap *E* was closed during removal of air from the apparatus by evacuation, thus preventing flow of mercury into *B* if a pressure difference existed between *A* and *B*. Tap *F*, normally kept closed, permitted equalisation of pressures in *A* and *C* when necessary. The volume of solution undergoing electrolysis was controlled by the level of the mercury overflow tube in *B* and that of the capillary jet terminating at the upper surface of the solution. Vessel *C* accommodated excess of *leuco*-solution and formed a trap preventing diffusion of any residual oxygen into *A*; it was provided with a mercury-filled bubbler gas outlet to *Z*. The lower end of *D*, containing *leuco*-solution, acted as a gas bubbler and oxygen trap. All of the smaller ground-glass joints were water-sealed against air-leakage. The previously boiled-out potassium chloride solution in the U-tube was thoroughly degassed by repeated evacuation in the assembled apparatus, thus



preventing the development of gas bubbles and a high electrical resistance at the glass stopper. After filling of the lower part of the apparatus with mercury, a similar degassing was required, to prevent an air-lock developing in tap *E*.

The polarograph, associated apparatus and materials used were as described in Part IV.[1]

Procedure.—Reduction of dye to give 25 ml. of *ca.* 10^{-3}M-*leuco*-solution in 48% v/v aqueous ethanol containing 0·1N-sodium hydroxide was performed as described previously for macro-polarography.[1] Before the reduction, the entire apparatus was evacuated and flushed with hydrogen three times to remove air; after reduction, the electrolysis cell alone was evacuated and flushed twice. With tap *E* closed, *leuco*-solution was forced by hydrogen pressure from the reduction vessel through the glass-wool filter and tube *X* into the cell, and followed by a little hydrogen through tube *Y* to ensure displacement of excess of solution into *C*. Tap *E* was then opened and tap *F* momentarily opened to equalise pressures in *A* and *C*. The glass-wool filter was well compacted, since incomplete removal of catalyst from the solution would lead to reduction of polarographically oxidised dye, with consequent high n values.

The solution in the cell was electrolysed at a potential corresponding to the diffusion–current plateau. At intervals, the complete polarographic wave was recorded to determine the wave-height. The recording took 2 min., during which the average current within one

drop-life fell from a maximum to zero, and was taken to be equivalent in effect to electrolysis for 1 min. at the maximum value.

The Gilbert–Rideal method for determining n involves the assumption that the wave-height falls only during electrolysis. For most *leuco*-solutions examined, however, the wave-height fell even when no current was passing, but less rapidly than during electrolysis. This is probably an oxidation effect. In some experiments the non-electrolytic fall occurred only when mercury flowed from the dropping electrode, and could be obviated temporarily by washing the mercury with dithionite solution to remove the oxidant (presumably a mercury oxide) responsible. Various well-known mercury-purification procedures led to only a brief improvement. In some other experiments the non-electrolytic decrease was rapid and practically independent of whether mercury was flowing; the presence of residual traces of some oxidant impurity cannot be excluded as an explanation here. A possible source of oxidant is air gradually evolved from the poly(vinyl chloride) tubing; this material is known to degas continuously under a vacuum.[5]

In general, the graphs of log i against t consisted of three linear sections, the first (pre-electrolysis period) being parallel to the third (post-electrolysis) and less steep than the second (electrolysis period). Hence the non-electrolytic decrease of i follows first-order kinetics, as does the electrolytic decrease. The difference between the slopes of the first and the second section thus gives the rate of change of log i due solely to electrolysis. This residual slope was inserted in the equation to determine n. Occasionally the pre-electrolysis graph exhibited initial curvature, generally associated with failure of the mercury drops from the electrode to coalesce, probably because of the presence of oxidant impurities in the cell. In such cases, no electrolysis was attempted until the graph became linear.

After periods of electrolysis and pre- and post-electrolysis long enough to permit accurate determination of the slopes of the three sections of the graph, the solution in A was removed with a capillary pipette and weighed. Its volume was calculated from its density, which was assumed to be the same for all the solutions electrolysed, and was determined for one of them with a hydrometer.

The direct determination of the true zero polarographic current line was not permitted by the characteristics of the Tinsley polarograph used. The zero line was at first assumed to coincide at any stage of the electrolysis with the bottom of the polarographic wave, which was taken to be wholly anodic. During the electrolysis of the benzamidoanthraquinols, however, the bottom as well as the top of the wave shifted towards lower current values. This, together with the high n values calculated on the assumption of a completely anodic wave, suggested that the oxidised dye was appreciably soluble in the ethanolic solvent (confirmed spectrophotometrically) and thus contributed a cathodic portion to the total wave-height. To correct for this, it was assumed that the freshly prepared *leuco*-solution was free from quinone, so that the first polarogram recorded was entirely anodic, the bottom of the wave coinciding with the zero-current line. The correction to the instrument zero thus obtained was applied unchanged to subsequent polarograms except when an alteration of the instrument sensitivity was necessary; in the latter eventuality, polarograms were recorded immediately before and after the alteration so that the zero-current correction for the new sensitivity could be determined.

Most of the *leuco*-solutions after electrolytic or pre-electrolytic oxidation tended to prevent coalescence of the mercury drops falling from the electrode, probably owing to strong adsorption of dye quinone on the drop surfaces. When severe, this effect led to a piling up of the discrete drops in the cell, without the normal overflow of mercury, until the cell became short-circuited and electrolysis was prohibited. When it was less severe, the drops coalesced after a few minutes or on tapping the cell; although with care electrolysis was then possible, the cell solution tended to become trapped between the mercury drops and carried below the mercury surface, thus decreasing the volume of solution electrolysed. Since the rate of electrolytic oxidation is proportional to *leuco*-dye concentration, drop-piling during electrolysis was minimised by keeping the concentration to the minimum consistent with the production of satisfactory polarograms; even so, with some dyes it was still necessary to tap the cell periodically during the earlier stages of electrolysis to induce coalescence. Pre-electrolytic oxidation by impurities was most evident after the apparatus had remained unused for some time, or had been cleaned and refilled with fresh mercury. Since in these circumstances oxidation of mercury was apparently responsible, the mercury surface was cleaned by filling

[5] Gore, *J. Sci. Instr.*, 1957, **34**, 459.

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the cell with warm alkaline dithionite and after some time rinsing with water. Any remaining pre-electrolysis piling was allowed to subside before measurements were started. Attempts to minimise drop-piling by adding various cationic, anionic, and non-ionic surface-active agents to the solution had little success.

Preparation of Electrolysis Products of Halogenated leuco-*Dyes for Spectroscopic Examination.*—To obtain the maximum quantity of each product under polarographic conditions, separate electrolyses were carried out in the micro-cell in which electrolysis started immediately after introduction of the *leuco*-solution and was continued until oxidation was almost complete. The solution was then exposed to air in the dark to complete oxidation without photo-dehalogenation, and the resulting suspension removed with a micro-pipette. The mercury in the cell was thoroughly washed with water injected beneath its surface, in order to recover the appreciable quantity of solid product carried below the mercury surface by drop-piling, which occurred with all the halogenated dyes. The combined washings and suspension removed from the cell were extracted with a minimum quantity of boiling chlorobenzene, and the extract was dried (CaO). The small volume of very dilute chlorobenzene solution thus obtained was placed on a layer of 5 ml. of mercury in a 4 cm. absorption cell, and its visible absorption spectrum determined with the Hilger Uvispek instrument, the aperture being used to limit the light beam so that it cleared the mercury. Both conventional (solvent in reference cell) and differential [6] spectra (solution of original dye, adjusted to the same concentration as in the test sample, in reference cell) were obtained.

Results

A typical complete set of electrolysis results is given for Caledon Gold Orange G in Table 1, and the results for all the dyes examined are summarised in Table 2.

Algol Yellow WG gave initially n values of about 1·0. Spectrophotometric examination of the electrolysis product disclosed no evidence of decomposition. Thus the low n values were probably due to the presence of considerable impurity in the dye sample. With a specially synthesised and purified sample,[1] the expected value $n = 2$ was obtained.

TABLE 1. *Electrolysis of* leuco-*Caledon Gold Orange G.*

0·28 ml. of *leuco*-solution, initial concn. 0·855 × 10^{-3}M, electrolysed at −0·3 v *vs.* S.C.E. Initial wave-height 2·60 μA.

t/60 (min.)	0	30 [a]	65	95	125	155	195	225	255 [b]
$10^6 i$ (A)	2·60	2·60	2·52	2·44	2·36	2·24	2·20	2·16	2·08
t/60 (min.)	285	315	345	375	420 [c]	455	485	515	
$10^6 i$ (A)	1·84	1·62	1·42	1·26	1·12	1·07	1·04	1·00	

[a] Hg flow started. [b] Electrolysis started. [c] Electrolysis ceased.

$-$d log i/dt before electrolysis 0·074 × 10^{-4} sec.$^{-1}$
" during " 0·305 " "
" after " 0·082 " "
" due to " 0·231 " "

$$n = 2{\cdot}60 \times 10^{-6}/2{\cdot}303 \times 0{\cdot}855 \times 10^{-3} \times 0{\cdot}28 \times 10^{-3} \times 96{,}500 \times 0{\cdot}231 \times 10^{-4} = 2{\cdot}12.$$

Cibanone Golden Yellow RK gave during one electrolysis a wave which, after initially decreasing in height, then increased several-fold rapidly; concurrently, mercury piling, normally severe with this dye, ceased completely, and the electrode drop-time increased considerably. In other runs the abnormally large wave-height appeared as soon as electrolysis started. The abnormalities disappeared when the vatting temperature was lowered from 65° to 45° for this dye, which the manufacturers recommend should be cold-vatted. The enhanced waves appear to be catalytic. Wiesner [7] obtained catalytic waves during the polarographic oxidation of quinol and other reduced substances in the presence of hydrogen and a palladium catalyst, owing to reduction by active hydrogen of the anodic oxidation product as it was formed at the electrode. In view of the lengthened drop-time and the use of a filter to remove catalyst, this explanation is unlikely here.

All the dyes examined possess two reducible nuclear carbonyl groups per molecule (for the indanthrones Cibanone Blue RSN and Caledon Blue RC, only two of the four keto-groups are

[6] Cooper and Stonehill, *J.*, 1958, preceding paper.
[7] Wiesner, *Z. Elektrochem.*, 1943, **49**, 164.

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normally reduced). The coulometric value $n = 2$ obtained for many of the dyes (Table 2) is thus as expected. For those halogenated *leuco*-dyes which undergo photo-dehalogenation,[6] n is about 1, suggesting partial dehalogenation during electrolysis. The conventional and differential visible absorption maxima of the electrolysis products of four of the latter dyes are given in Table 3, along with comparative data for the original dyes and their unhalogenated

TABLE 2. *Summary of results of oxidative coulometry.*

Dye	i_0/c	10^3v	-10^5 d log i/dt before electrolysis	-10^5 d log i/dt during electrolysis	n
Algol Yellow WG	4·65	0·45	0·67	2·90	2·08
		0·30	0·85	4·24	2·06
Caledon Red 5G	4·46	0·43	0·82	2·95	2·17
		0·47	0·27	2·22	2·19
Caledon Red X5BS	4·10	0·32	0·00	2·72	2·11
Anthanthrone	5·45	0·23	0·12	5·28	2·07
		0·36	0·49	4·03	1·93
Cibanone Brilliant Orange GK [a]	3·00	0·27	0·73	6·35	0·89
		0·26	2·23	8·00	0·90
		0·28	1·17	5·97	1·00
Caledon Brilliant Orange 6R [a]	3·89	0·34	0·03	5·54	0·94
		0·29	0·41	7·06	0·91
		0·30	0·44	5·98	1·05
Cibanone Golden Yellow GK	4·32	0·36	0·25	2·72	2·18
		0·29	0·91	3·98	2·18
Cibanone Golden Yellow RK [a]	3·01	0·32	0·28	4·71	0·96
		0·27	0·73	6·05	0·94
Caledon Gold Orange G	3·04	0·28	0·74	3·05	2·12
		0·26	0·56	3·54	1·77
		0·28	0·58	2·96	2·05
Caledon Orange 2RTS [a]	2·48	0·31	0·16	3·90	0·97
		0·26	0·00	4·50	0·95
Caledon Brilliant Orange 4RN [b]	1·96	0·46	2·29	4·31	0·95
		0·38	2·29	4·91	0·89
		0·30	3·79	6·83	0·96
Cibanone Blue RSN	3·74	0·26	0·56	3·77	2·01
		0·37	2·62	4·62	2·27
		0·33	3·00	5·61	1·96
Caledon Blue RC	3·62	0·41	2·18	4·26	1·91
		0·29	2·19	4·75	2·19

[a] Photoactive. [b] Photoactive; electrolysed for only ½ hr. owing to mercury-piling.

TABLE 3. *Absorption maxima of* leuco*-dye electrolysis products.*

[Wavelengths of conventional (λ_c) and differential (λ_d) maxima are given in mμ, with optical densities (4 cm. cells) in parentheses. Differential maxima were obtained by placing in the reference cell a solution of the original dye, adjusted to the concentration at which it was present in the test sample; the absorption maxima of this reference solution are given under the last column heading.]

Dye	Electrolysis product λ_c	Electrolysis product λ_d	Unhalogenated analogue λ_c	Original dye λ_c
Cibanone Brilliant Orange GK	492 (0·89)	480 (0·21)	478	492 (0·80)
	463 (0·71)	450 (0·15)	450	465 (0·55)
Caledon Brilliant Orange 6R	490 (0·55)	480 (0·15)	478	492 (0·45)
	461 (0·48)	450 (0·09)	450	462 (0·39)
Caledon Orange 2RTS	487 (0·41)	473 (0·10)	474	488 (0·39)
	455 (0·23)	442 (0·06)	443	456 (0·20)
Cibanone Golden Yellow RK	471 (1·14)	466 (0·28)	466	473 (0·95)
	442 (0·83)	436 (0·18)	436	443 (0·70)

analogues.[6] The conventional maxima of the electrolysis products exhibit a slight hypsochromic shift of 1—2 mμ towards those of the unhalogenated analogues, but the results are inconclusive, since the concentrations and thus the absorbancies were low, leading to broad maxima with uncertain peak wavelengths. The differential absorption maxima, however, provide positive proof of partial dehalogenation. The optical densities of the differential

maxima are *ca.* ⅓—½ of those of the corresponding maxima of the reference solutions of the original dyes. If similar molar extinction coefficients are assumed for the original dye and the unhalogenated analogue, this suggests that about 20—25% of dehalogenation has occurred. For *leuco*-Caledon Brilliant Orange 4RN the preparation for spectroscopic investigation of a sample of the exhaustive electrolysis product was impossible, owing to severe mercury-piling after about ½ hour's electrolysis.

Discussion

The dehalogenation accompanying electrolysis of the photo-active *leuco*-dyes must occur either during or after the electrolysis, which, under the conditions employed, yields exclusively dye quinones at the dropping-mercury electrode surface. These dyes are all strongly adsorbed on the electrode, as shown by the adsorption waves obtained during macro-polarography,[1] as well as by the particularly pronounced mercury-piling during micro-polarography. The diffusion current constants [1] indicate that the electrode reaction corresponds to $n = 2$. The apparent value $n = 1$ thus requires that half of the *leuco*-oxidation is electrochemical, the other half being chemical and occurring well away from the electrode surface in order not to affect the diffusion of fresh *leuco*-dye to the electrode. The 25% dehalogenation observed necessitates that water be decomposed to provide hydrogen which replaces halogen. The overall process may thus be written:

$$2X_2R(O^-)_2 + H_2O - 2e \longrightarrow 1\tfrac{1}{2}X_2RO_2 + \tfrac{1}{2}H_2RO_2 + X^- + OH^-$$

with a corresponding equation for the tautomeric oxanthranol:

$$2O{:}RX_2H{\cdot}OH + 3OH^- - 2e \longrightarrow 1\tfrac{1}{2}X_2RO_2 + \tfrac{1}{2}H_2RO_2 + X^- + 3H_2O$$

The following mechanism is tentatively suggested. The mercury abstracts a halogen atom from a dye molecule adsorbed on the electrode, forming mercury halide, whilst a water molecule in the solvent sheath or hydration shell releases a hydrogen atom to replace the halogen, producing a hydroxyl radical. This process may occur either during the bivalent electrolytic oxidation of adsorbed quinol (or oxanthranol):

$$X_2R(O^-)_2 + H_2O + Hg - 2e \longrightarrow HXRO_2 + HgX + OH\cdot$$

or after the electrolytic oxidation:

$$X_2R(O^-)_2 - 2e \longrightarrow X_2RO_2$$
$$X_2RO_2 + Hg + H_2O \longrightarrow HXRO_2 + HgX + OH\cdot$$

The mercury-piling effect might be due at least in part to the HgX film on the drop surface. The products thus formed diffuse away from the electrode or are carried away by the falling mercury drop. The hydroxyl radical and the mercury halide are capable of, and stoicheiometrically sufficient for, oxidation of a further molecule of dye quinol (or oxanthranol):

$$X_2R(O^-)_2 + OH\cdot + HgX \longrightarrow X_2RO_2 + OH^- + Hg + X^-$$

As before,[6] the monohalogenated dye is presumed to disproportionate:

$$HXRO_2 \longrightarrow \tfrac{1}{2}H_2RO_2 + \tfrac{1}{2}X_2RO_2$$

In connection with this and the two preceding papers we thank Imperial Chemical Industries Limited, Dyestuffs Division, The Clayton Aniline Company Limited, Bernard Keegan and Company, and Brothertons Limited for gifts of materials.

Medway College of Technology, Chatham, Kent.
[*Present Addresses.*—(C. J. C.) Municipal College of Technology and Commerce, Bournemouth,
(H. I. S.) Royal Military College of Science, Shrivenham, Wilts.]
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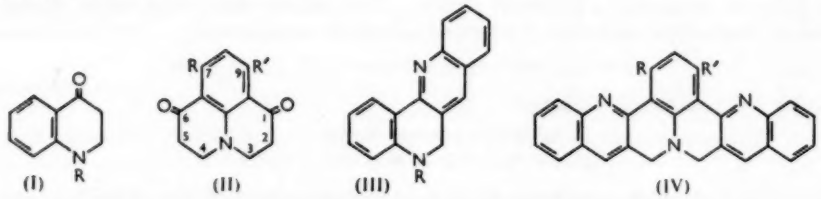
682. *The Structure and Properties of Certain Polycyclic Indolo- and Quinolino-derivatives. Part X.* Some Applications of the Friedländer Reaction, and Further Studies of the Quinolino-bases Prepared from Cyclic Keto-amines.*

By JOHN T. BRAUNHOLTZ and FREDERICK G. MANN.

Certain cyclic keto-amines, previously studied, react with *o*-aminobenzaldehyde under very mild conditions to give the corresponding quinolino-derivatives in good yields. New evidence is adduced to support the structures assigned earlier to these compounds when obtained under the more vigorous conditions of the Pfitzinger reaction, followed by decarboxylation. The rather difficult allylic rearrangement of 1 : 2-dihydro-1-phenylquinolino-(3′ : 2′-3 : 4)quinoline has been shown to proceed similarly to that of its 1-methyl analogue. The structures of the two allylic isomers, 1 : 2- and 1 : 4′-dihydro-1-methylquinolino(3′ : 2′-3 : 4)quinoline, have been placed beyond doubt by measurements of infrared and nuclear magnetic resonance spectra. 1 : 2-Dihydro-1-toluene-*p*-sulphonylquinolino(3′ : 2′-3 : 4)quinoline and 3′ : 4′-dihydronaphtho(1′ : 2′-2 : 3)quinoline do not undergo the allylic rearrangement.

EARLIER papers in this series [1,2,3] describe the reaction of keto-amines such as 1 : 2 : 3 : 4-tetrahydro-1-methyl-4-oxoquinoline (I; R = Me) and 1 : 6-dioxojulolidine (II; R = R′ = H) with isatin in ethanolic alkali to give quinolino-4′-carboxylic acids, from which the quinolino-bases (*e.g.*, III; R = Me; and IV; R = R′ = H) were obtained by decarboxylation. The allylic isomerisation which these bases undergo when heated with acids, and the ready oxidation to cyclic amides which both isomers derived from the quinoline (I; R = Me) undergo, have also been discussed.[2]



(I) (II) (III) (IV)

The carboxylic acid (VI; R = CO_2H) obtained similarly by the Pfitzinger reaction from the tetrahydro-4-oxoarsinoline (V) resisted decarboxylation, however, and the corresponding quinolino-base (VI; R = H) was obtained by the reaction of the ketone (V) with *o*-aminobenzaldehyde.[4] The Friedländer reaction has now been applied to a number of ketones of types (I) and (II), with the object of preparing their derivatives (III) and (IV) under the mildest possible conditions, and therefore with the least risk of allylic rearrangement. In addition, the Friedländer reaction provides a very convenient method for the rapid preparation of these quinolino-bases on a larger scale and in a higher degree of initial purity than hitherto.

7 : 9-Dimethyl-1 : 6-dioxojulolidine (II; R = R′ = Me) with an excess of *o*-aminobenzaldehyde at room temperature gives 7 : 9-dimethyl-6-oxoquinolino(2′ : 3′-1 : 2)-juloline (VII; R = R′ = Me); the base gives a 2 : 4-dinitrophenylhydrazone, and its infrared spectrum contains the C=O absorption band at 1672 cm.$^{-1}$, close to that at

* Part IX, *J.*, 1957, 3352.

[1] Mann, *J.*, 1949, 2816.
[2] Braunholtz and Mann, *J.*, 1955, 381.
[3] *Idem*, *J.*, 1955, 393.
[4] Mann and Wilkinson, *J.*, 1957, 3346.

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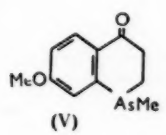
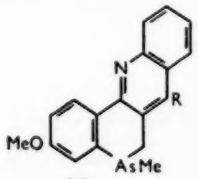
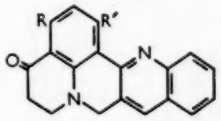
1668 cm.$^{-1}$ of its 7-methyl analogue [5] (VII; R = Me, R′ = H). Whereas we find no evidence of the formation of the diquinolino-compound (IV; R = R′ = Me) from the diketone (II; R = R′ = Me), 7-methyl-1 : 6-dioxojulolidine (II; R = Me, R′ = H) reacts readily with two molecules of *o*-aminobenzaldehyde, yielding 7-methyldiquinolino(2′ : 3′-1 : 2)(3″ : 2″-5 : 6)juline (IV; R = Me, R′ = H), an intensely yellow base; and 1 : 6-dioxojulolidine similarly gives the bright orange diquinolino(2′ : 3′-1 : 2)(3″ : 2″-5 : 6)juline [3] (IV; R = R′ = H). In both these cases, however, the initial ethanol-insoluble crude products show strong infrared absorption in the region of 1670 cm.$^{-1}$, close to the bands recorded above for the bases (VII; R = Me, R′ = Me or H); furthermore, both crude products, when heated in pyridine change markedly in appearance, and the compound (IV; R = R′ = H) when thus purified is identical with that described earlier.[3] It is possible that in the initial product one or both of the dioxojulolidine carbonyl groups are free and finally condense with ring-closure only at a higher temperature.



(V)



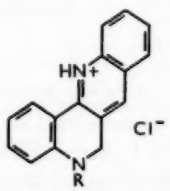
(VI)



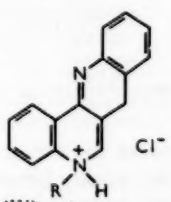
(VII)

It is noteworthy that the quinolino-bases (VII; R = R′ = Me) and (IV; R = Me, R′ = H) cannot be obtained from the corresponding dioxojulolidines by the Pfitzinger route, which gives no product with the diketone (II; R = R′ = Me), and only the monoquinolino-derivative (VII; R = Me, R′ = H) with the 7-methyl-diketone [5] (II; R = Me, R′ = H). It therefore appears that, under the conditions of these experiments, the nuclear methyl groups exert a markedly greater steric obstruction to the Pfitzinger than to the Friedländer reaction. It is noteworthy that Buu-Hoï and Cagniant have shown that, although 1-acetyl-2-methylnaphthalene reacts with alkaline isatin, its 2-ethyl analogue does not.[6]

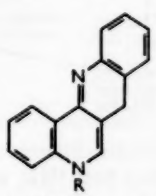
The 1 : 2 : 3 : 4-tetrahydro-4-oxoquinolines (I; R = Me [7] and Ph [1,8]) also react readily with *o*-aminobenzaldehyde at room temperature, giving 1 : 2-dihydro-1-methylquinolino(3′ : 2′-3 : 4)quinoline [2] (III; R = Me) and its 1-phenyl analogue [1] (III; R = Ph). The quinolinoquinolines obtained are identical with those prepared earlier by decarboxylation of the 4′-carboxylic acids obtained by the reaction between the keto-amines (I; R = Me or Ph) and alkaline isatin. Their formation in good yield under the



(VIII)



(IX)



(X)

very mild conditions of the Friedländer reaction gives strong supporting evidence for the structures originally assigned to the bases (III; R = Me or Ph), and in particular for the position of the sole cyclic methylene group which they both contain.

[5] Ittyerah and Mann, *J.*, 1958, 467.
[6] Buu-Hoï and Cagniant, *Bull. Soc. chim. France*, 1946, 123.
[7] Allison, Braunholtz, and Mann, *J.*, 1954, 403.
[8] R. C. Cookson and Mann, *J.*, 1949, 67.

The rather difficult conversion of 1 : 2-dihydro-1-phenylquinolino(3′ : 2′-3 : 4)quinoline[1] (III; R = Ph), *via* its deep red monohydrochloride (VIII; R = Ph), into the yellow monohydrochloride (IX; R = Ph) of the allylic isomeric base (X; R = Ph) was briefly recorded earlier.[2] It is now found that this isomerisation proceeds satisfactorily in boiling concentrated hydrochloric acid containing a small quantity of dioxan; the yellow salt (IX; R = Ph) is thus readily available, and the 1-phenylquinolino-series of compounds

FIG. 1. FIG. 2.

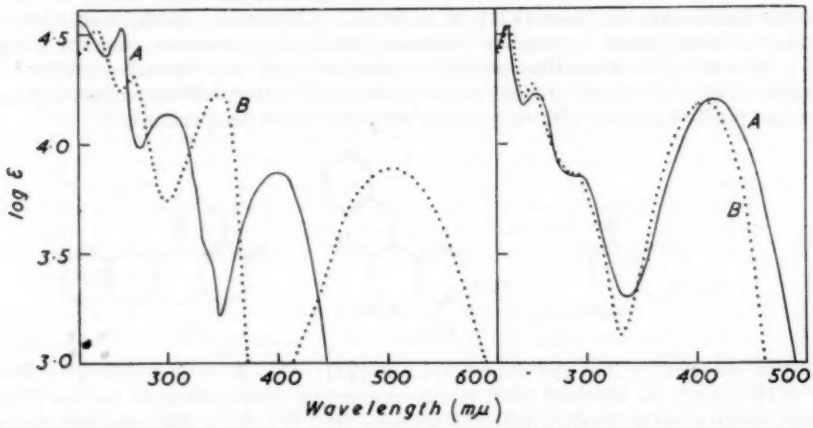
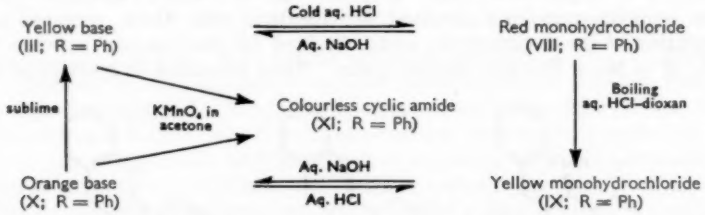


FIG. 1. *Ultraviolet spectra of* 1 : 2-*dihydro*-1-*phenylquinolino*(3′ : 2′-3 : 4)*quinoline* (III; R = Ph) *in* (*A*) *ethanol*, (*B*) 1 : 1 *ethanol–*N*-hydrochloric acid*: *there is a minimum in* (*B*) *at* 380 mμ (log ε 2·255) *not shown.*

FIG. 2. *Ultraviolet spectra of* 1 : 4′-*dihydro*-1-*phenylquinolino*(3′ : 2′-3 : 4)*quinoline* (X; R = Ph) *in* (*A*) *ethanol*, (*B*) 1 : 1 *ethanol–*N*-hydrochloric acid.*

[*For the above spectra, and those in Figs.* 4 *and* 5, *the ethanol used contained* 5% *of water.*]

clearly undergoes a cycle of changes of the same nature as those in the 1-methylquinolino-series;[2] these may be summarised as in the annexed scheme.



Three particular differences between the 1-methyl and 1-phenyl series may be noted: (*a*) The quinolino-base (III; R = Me) readily forms a colourless, rather unstable, dihydrochloride,[2] but the analogous 1-phenyl compound (III; R = Ph) forms only the red mono-salt under the corresponding conditions, owing to the reduced basic strength of the 1-amino-group. (*b*) When the conversion of the salt (VIII; R = Ph) into its isomer (IX; R = Ph) is attempted in ethanolic hydrochloric acid, an insoluble plum-coloured monohydrochloride is obtained. This salt is probably a dimorphic form of the yellow hydrochloride (IX; R = Ph), for their infrared spectra are almost identical, whereas that of the former differs markedly from that of the red hydrochloride (VIII; R = Ph). Basification of the intermediate hydrochloride gives the crude orange base (X; R = Ph). An analogous

example of apparent dimorphism occurring during the acid-catalysed rearrangement of the Pfitzinger acids derived from 1 : 2 : 3 : 4-tetrahydro-1-methyl-4-oxoquinoline (I; R = Me) has been noted earlier.[2] (*c*) The orange quinolino-base (X; R = Ph) differs from the corresponding 1-methyl compound (X; R = Me) in being amorphous instead of highly crystalline, and its purification by recrystallisation has proved impossible, possibly owing to rapid atmospheric oxidation. The base (X; R = Ph) is also unusual in that its m. p. is below that of its precursor (III; R = Ph), into which it is converted by vacuum-sublimation (cf. X; R = Me).

The close analogy between the 1-methyl and the 1-phenyl series of interconvertible quinolino-derivatives (*e.g.*, III and X) is, however, emphasised by a comparison of the ultraviolet absorption curves for the latter (III and X; R = Ph) in ethanolic and acidic

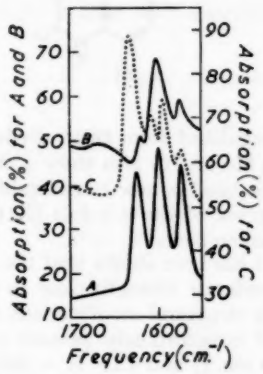


FIG. 3. *Infrared spectra of (A) quinoline (in liquid film) and of the quinolino-bases* (III; R = Me) (*B*) *and* (X; R = Me) (*C*), *in Nujol mull, in the region* 1550—1700 *cm.*$^{-1}$.

solution (Figs. 1 and 2), with those for the 1-methyl compounds recorded earlier,[2] when the structural evidence derived from these spectra was discussed.

Infrared spectra (*cm.*$^{-1}$) *of certain polycyclic derivatives of quinoline in the region* 1570—1650 *cm.*$^{-1}$ (*in Nujol mull, unless otherwise stated*).

Quinoline *	1623(m)	1598 (s)	1574 (m)	
(III; R = Me)	1620 (w)	1602 (m)	1574 (w)	
(III; R = Ph)	1620 (w)	1598 (m)	1576 (w)	
(III; R = SO_3·C_6H_4·Me)	1618 (w)	1600 (m)	1580 (w)	
(XIII; R = H)	1620 (w)	1601 (m)	1578 (w)	
(IV; R = R′ = H)	1618 (m)	1601 (s)	1577 (m)	
(XII)	1639 (s)	1600 (s)		
(X; R = Me)	1631 (s)	1607 (m)	1593 (m)	1574 (w)
(X; R = Ph)	1632 (s)	1608 (w)	1593 (m)	1577 (w)
(III or X; R = H) †	1629 (m)	1618 (m)	1575 (s)	
Isomer of (IV; R = R′ = H)	1647 (m)	1626 (w)	1600 (m)	1575 (w)

* Liquid film. † There is some uncertainty concerning the structure of this base; although the positions of the bands are similar to those in the first group, their relative intensities show a markedly different distribution.

Further evidence for the structures of the quinolino-bases (III), (IV), and (X) has been obtained from their infrared spectra and, of particular importance in the case of the isomeric compounds (III; R = Me) and (X; R = Me), from their nuclear magnetic resonance spectra also.

The absorption bands between 1570 and 1650 cm.$^{-1}$ in the infrared spectra of the quinolino-bases are summarised in the Table, with those of quinoline and of 1-methyl-ψ-indolo(3′ : 2′-3 : 4)quinoline [2] (XII); the significant features are illustrated (Fig. 3) by a comparison of the infrared spectrum of quinoline with those of the isomeric quinolino-bases (III; R = Me) and (X; R = Me).

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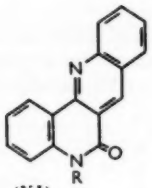
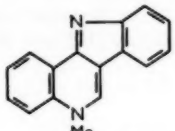
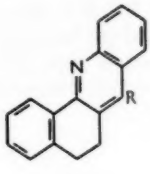
It is clear that in this region of the infrared spectrum, characterising the C=C and C=N– groups, the bases (*e.g.*, III, IV, XIII) initially obtained by Friedländer or Pfitzinger reactions[8] give rise to a band pattern which is remarkably constant in position and distribution of intensities. This constancy emphasises the structural similarities between the bases, and the pattern itself, which appears to arise from the true (unhydrogenated) quinolino-portion of the compounds, provides a diagnostic test whereby they may be


(XI)


(XII)


(XIII)

distinguished from their allylic isomers. The spectra of the latter derivatives (*e.g.*, X; R = Me or Ph) also show a characteristic pattern in the 1570—1650 cm.$^{-1}$ region; the major band is now considerably above 1600 cm.$^{-1}$, and the similarities with the infrared spectrum of the ψ-indole (XII) are in accordance with the proposed structures of the quinolino-bases.

It has been shown that the free >NMe group gives rise to an infrared absorption band of moderate strength close to 2800 cm.$^{-1}$, which disappears or becomes extremely weak when structural modifications involving the nitrogen lone pair of electrons occur.[9] This band is accordingly present in the spectra of the isomeric bases (III; R = Me) (at 2790 cm.$^{-1}$) and (X; R = Me) (at 2795 cm.$^{-1}$) but absent from that of their common oxidation product (XI; R = Me), thus confirming its cyclic amide structure. Further, it is present in the spectrum of the red monohydrochloride (VIII; R = Me) of the base (III; R = Me) (at 2790 cm.$^{-1}$), and thus confirms that salt formation has not occurred at the >NMe group; on the other hand, it is absent from the spectrum of the yellow monohydrochloride (IX; R = Me) of the isomeric base (X; R = Me), showing that in this salt protonation has occurred on the >NMe group and not at position 1'.

Hitherto there has been no physical method available by which the structures of our isomeric bases could be decisively differentiated with respect to the location of the solitary methylene group at position 2 in one base (*e.g.*, III; R = Me) and at position 4' in the other (*e.g.*, X; R = Me), or *vice versa*. Dr. Sheppard has kindly investigated the nuclear magnetic resonance spectra of these bases in pyridine solution, and reports:

" The high-resolution hydrogen nuclear magnetic resonance spectra of the two compounds were taken in " AnalaR " pyridine solution, with *cyclo*hexane as an external standard; a Varian Associates 4300 B spectrometer was used with a frequency of 40 Mc., and the resonances of the hydrogen atoms in the saturated groupings >CH_2 and –CH_3 were studied. In each case, two sharp peaks were observed, of relative intensities 3 : 2, which could clearly be assigned to the >N–Me group and the methylene group respectively. The chemical shifts were measured relative to *cyclo*hexane, assumed to be +3·9 parts per million relative to water. The chemical shifts in the case of base (III; R = Me) were 2·9 for the >N–Me group and 1·6 for the methylene group. In the case of base (X; R = Me), the corresponding chemical shifts were 2·5 and 1·8 respectively. The relative values of these chemical shifts agree well with expectations based on the two formulæ given. In particular, the lower value of the >N–Me chemical shift of base (X; R = Me) is to be expected because of the extra double bond immediately adjacent to the nitrogen atom." [10]

[9] Braunholtz, Ebsworth, Mann, and Sheppard, *J.*, 1958, 2780.
[10] Wertz, *Chem. Rev.*, 1955, **55**, 829.

It is especially noteworthy that this confirmation of the structures (III and X; R = Me) is extended, by the interrelations between the infrared spectra of the quinolino-derivatives discussed above, to all the bases of types (III) and (X), whose structures are thereby confirmed.

Further evidence for the factors which determine the interannular allylic isomerisation in compounds such as (III; R = Me or Ph) has been obtained by investigating the quinolino-bases (III; R = $\cdot SO_2 \cdot C_6H_4Me$) and (XIII; R = H).[11]

1 : 2 : 3 : 4-Tetrahydro-4-oxo-1-toluene-*p*-sulphonylquinoline [12] (I; R = $SO_2 \cdot C_6H_4Me$) reacts readily with *o*-aminobenzaldehyde to give 1 : 2-dihydro-1-toluene-*p*-sulphonylquinolino(3′ : 2′-3 : 4)quinoline (III; R = $SO_2 \cdot C_6H_4Me$). This cream-coloured base forms a rather unstable yellow hydrochloride; treatment with boiling dilute hydrochloric acid, a process which causes rapid isomerisation of the 1-methyl base (III; R = Me), leaves the derivative (III; R = $SO_2 \cdot C_6H_4Me$) unchanged, but prolonged boiling with concentrated

FIG. 4. FIG. 5.

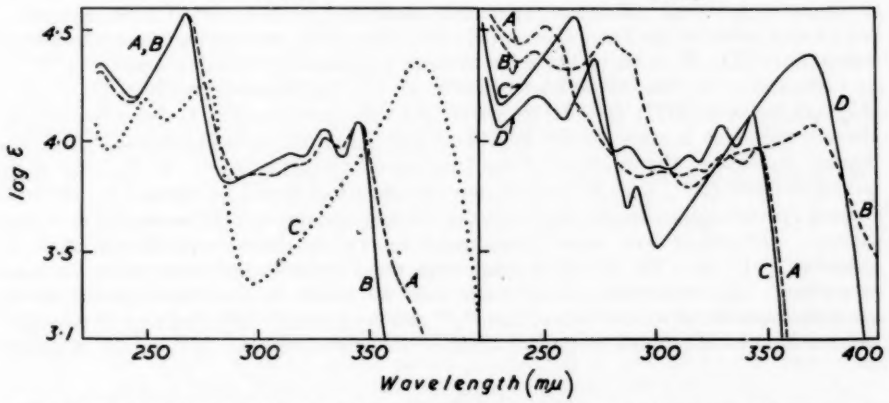


FIG. 4. *Ultraviolet spectra of* 3′ : 4′-*dihydronaphtho*(1′ : 2′-2 : 3)*quinoline-4-carboxylic acid* (XIII; R = CO_2H) (*A*) *in ethanol,* (*B*) *in* 1 : 1 *ethanol–*0·1N-NaOH *and* (*C*) *in* 1 : 1 *ethanol–*N-*hydrochloric acid.*

FIG. 5. *Ultraviolet spectra of* 1 : 2-*dihydro*-1-*toluene*-p-*sulphonylquinolino*(3′ : 2′-3 : 4)*quinoline* (III; R = $SO_2 \cdot C_6H_4Me$) (*A*) *in ethanol and* (*B*) *in* 1 : 1 *ethanol–*0·1N-*hydrochloric acid, and of* 3′ : 4′-*dihydronaphtho*(1′ : 2′-2 : 3)*quinoline in* (*C*) *ethanol and* (*D*) 1 : 1 *ethanol–*N-*hydrochloric acid.*

hydrochloric acid removes the toluene-*p*-sulphonyl group, and the monohydrochloride (probably IX; R = H) [2] of the base (III, R = H; or X, R = H), first prepared by Clemo and Perkin,[13] is obtained.

3′ : 4′-Dihydronaphtho(1′ : 2′-2 : 3)quinoline-4-carboxylic acid (XIII; R = CO_2H), prepared from α-tetralone by the Pfitzinger reaction,[11] differs in the following respects from the analogous carboxylic acids which are derived from the keto-amines (I; R = H, Me or Ph) and contain a basic nitrogen atom in the 1-position [corresponding to the 4′-position in the acid (XIII; R = CO_2H)].

(*a*) The acid (XIII; R = CO_2H) resembles the acid (VI; R = CO_2H) prepared from the 1 : 2 : 3 : 4-tetrahydro-4-oxoarsinoline [4] in being pale yellow, whereas the acids from the oxoquinolines are red: contribution by a canonical form similar in type to (XIV), which by stabilising a zwitterion structure might well give rise to an intense colour,[1,2] is in the first two acids impossible and improbable respectively.

(*b*) The ultraviolet spectra of the acid (XIII; R = CO_2H) in various media (Fig. 4) show that absorptions by the acid and its anion are almost identical, and closely resemble

[11] von Braun and Wolff, *Ber.*, 1922, **55**, 3675.
[13] Johnson, Woroch, and Buell, *J. Amer. Chem. Soc.*, 1949, **71**, 1901.
[13] Clemo and Perkin, *J.*, 1924, **125**, 1608.

XUM

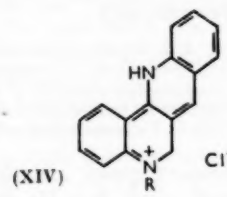
that of the derived base (XIII; R = H) (Fig. 5), whereas a slight shift to longer wavelength occurs on passing into an acidic medium. This evidence suggests strongly that the free acid is not a zwitterion.

(*c*) Evidence from the infrared spectrum of the acid is indecisive. Although there are strong bands present in the regions 1610—1550 and 1400—1300 cm.$^{-1}$,[14] there are also three broad regions of absorption centred at 3310, 2450, and *ca.* 2000 cm.$^{-1}$ which indicate an analogy with cinchoninic acid and quinaldinic acid which apparently exist as a non-zwitterionic structure exhibiting powerful hydrogen-bonding.[15]

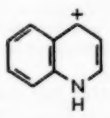
(*d*) The acid (XIII; R = CO_2H) sublimes unchanged when strongly heated at very low pressures; in this it again resembles the quinolino-acid (VI; R = CO_2H) derived from the oxoarsinoline,[4] but differs from those obtained from the oxoquinolines (III). Smooth decarboxylation is, however, effected by heating the acid at 14 mm.

The low-melting almost colourless dihydronaphthoquinoline (XIII; R = H) forms a pale yellow hydrochloride, which is unchanged even when boiled with concentrated hydrochloric acid for ten hours, and an allylic rearrangement analogous to the change (III ⟶ X) could not be achieved. Further, the base is unaffected by an excess of permanganate in hot acetone, whereas the bases (III and X; R = Me or Ph) are rapidly converted into the keto-amines (XI; R = Me or Ph), even at room temperature, by this reagent.

Comparison of the ultraviolet spectra of the quinolino-derivatives (III; R = $SO_2{\cdot}C_6H_4Me$) and (XIII; R = H) in neutral and acidic solution (Fig. 4) shows that protonation of each base is accompanied by a small but significant bathochromic shift and by a marked increase in the intensity of the long-wave absorption band. In the case of the quinolino-bases (III; R = Me or Ph), any similar effect would be masked by the more striking spectroscopic changes caused by the marked resonance (VIII) ⟷ (XIV) of their cations. This effect was noted previously[4] for the analogous quinolino(3′ : 2′-3 : 4)-arsinoline (VI; R = H), in which again only the 1′-quinolino-nitrogen atom has basic properties. The conversion of quinoline into its cation is also accompanied by an intensification of ultraviolet absorption,[16,17] and by a small shift to longer wavelength, which has been attributed to participation of structures such as (XV) in the resonance



(XIV)



(XV)

hybrid of the cation;[16] forms analogous to (XV) are presumably also responsible for the corresponding spectroscopic effects in the bases (III; R = $SO_2{\cdot}C_6H_4Me$) and (XIII; R = H).

A comparison of the above properties of the bases (III; R = $\cdot SO_2{\cdot}C_6H_4Me$) and (XIII; R = H) with those of the 1-methyl- and 1-phenyl-quinolino-analogues (III; R = Me or Ph) provides strong confirmation for our earlier suggestion[2] that the interannular allylic system of these polycyclic quinoline derivatives shows highly reactive tautomeric properties only if it is directly joined to a basic nitrogen atom. Other examples will be discussed later.[18]

Whereas this allylic rearrangement occurs in the direction (III) ⟶ (X) under the influence of acids, the reverse change (X) ⟶ (III) occurs when the free bases of type (X)

[14] Bellamy, " The Infrared Spectra of Complex Molecules," Methuen, London, 1956, pp. 206 ff.
[15] Braunholtz, Hall, Mann, and Sheppard, unpublished work
[16] Ewing and Steck, *J. Amer. Chem. Soc.*, 1946, **68**, 2181.
[17] Albert, Brown, and Cheeseman, *J.*, 1951, 474.
[18] Braunholtz and Mann, following paper.

sublime at low pressure and is presumably determined by the greater stability of the more highly aromatised isomer (III).

Experimental

To obtain consistent m. p.s, certain substances were heated in evacuated tubes (indicated as E.T.) with the immersion temperature noted as (I.T.).

The Ketones.—α-Tetralone was a purified technical sample. The preparative sources of the keto-amines are given in the references in the following section.

The Friedländer Reaction.—(*a*) In a typical reaction, a solution of 1 : 2 : 3 : 4-tetrahydro-1-methyl-4-oxoquinoline [7] (I; R = Me) (0·3 g.) in ethanol (3 c.c.) was treated with *o*-aminobenzaldehyde [4] (0·25 g., 1·1 mol.) and 10% aqueous sodium hydroxide (0·3 c.c.); the mixture was set aside at room temperature for 36 hr. under nitrogen, then diluted with water (1 c.c.); the crystalline deposit of 1 : 2-dihydro-1-methylquinolino(3′ : 2′-3 : 4)quinoline [2] (III; R = Me) (0·4 g., 87%) had m. p. 98—100° after crystallisation from ethanol (Found: N, 11·6. Calc. for $C_{17}H_{14}N_2$: N, 11·4%).

(*b*) The following Friedländer conversions were similarly effected, *ca.* 1·1 mol. of *o*-aminobenzaldehyde being used for each keto-methylene group: 1 : 2 : 3 : 4-Tetrahydro-4-oxo-1-phenylquinoline [8] (I; R = Ph) into 1 : 2-dihydro-1-phenylquinolino(3′ : 2′-3 : 4)quinoline [1] (III; R = Ph) (96%), m. p. 139—142° (from ethanol) (lit.,[1] 139—141°) (Found: N, 9·15. Calc. for $C_{22}H_{16}N_2$: N, 9·1%); 1 : 2 : 3 : 4-tetrahydro-4-oxo-1-toluene-*p*-sulphonylquinoline [19] (I; R = SO_2·C_6H_4Me) into 1 : 2-*dihydro*-1-*toluene*-p-*sulphonylquinolino*(3′ : 2′-3 : 4)*quinoline* (III; R = SO_2·C_6H_4Me) (47%), pale cream needles, m. p. 179° (from ethanol) (Found: C, 71·7; H, 4·85; N, 7·15. $C_{23}H_{18}O_2N_2S$ requires C, 71·5; H, 4·7; N, 7·25%); 1 : 6-dioxojulolidine [20, 21] (II; R = R′ = H) into diquinolino(2′ : 3′-1 : 2)(3″ : 2″-5 : 6)juline [5] (IV; R = R′ = H) (81%), m. p. 327° (E.T., I.T. 320°) (lit.,[5] m. p. 320°) (from pyridine) (Found: N, 11·15. Calc. for $C_{26}H_{17}N_3$: N, 11·3%); 7-methyl-1 : 6-dioxojulolidine [5, 21, 22] (II; R = Me, R′ = H) into 7-*methyldiquinolino*(2′ : 3′-1 : 2)(3″ : 2″-5 : 6)*juline* (cf. ref. 5) (IV; R = Me, R′ = H) (83%), intensely yellow needles, m. p. 275° (E.T., I.T. 265°) (from pyridine) (Found: C, 84·45; H, 4·95; N, 11·1. $C_{27}H_{19}N_3$ requires C, 84·2; H, 4·9; N, 10·9%); 7 : 9-dimethyl-1 : 6-dioxojulolidine [5] (II; R = R′ = Me) into 7 : 9-*dimethyl*-6-*oxoquinolino*(2′ : 3′-1 : 2)*juloline* (VII; R = R′ = Me) (cf. ref. 5) (50%), bright yellow platelets, m. p. 195° (E.T., I.T. 175°) (from ethanol) (Found: C, 80·4; H, 6·0; N, 9·05. $C_{21}H_{18}ON_2$ requires C, 80·3; H, 5·75; N, 8·9%).

3′ : 4′-*Dihydronaphtho*(1′ : 2′-2 : 3)*quinoline* (XIII; R = H).—(*a*) A solution of α-tetralone (3 g.) in aqueous ethanol (5 c.c./20 c.c.) containing potassium hydroxide (3·6 g.) was treated with isatin (3 g., 1 mol.), and boiled under reflux for 4·5 hr. The cold mixture, when poured into an excess of 10% aqueous acetic acid, deposited the crystalline 3′ : 4′-dihydronaphtho-(1′ : 2′-2 : 3)quinoline-4-carboxylic acid [11] (XIII; R = CO_2H) (4·25 g., 75%), very pale yellow crystals, m. p. 253° (effervescence) (from ethanol) (lit.,[11] m. p. 252°) (Found: N, 5·05. Calc. for $C_{18}H_{13}O_2N$: N, 5·1%).

(*b*) The acid (XIII; R = CO_2H) when heated at 250—280°/14 mm. underwent smooth decarboxylation without residue, giving 3′ : 4′-dihydronaphtho(1′ : 2′-2 : 3)quinoline [11] (XIII; R = H), m. p. 60° (from aqueous ethanol) (lit.,[11] m. p. 60°) (Found: N, 5·75. Calc. for $C_{17}H_{13}N$: N, 6·0%).

(*c*) The acid (XIII; R = CO_2H) sublimed unchanged at 210—220°/0·0001 mm.; the identity of the pale yellow crystalline sublimate, m. p. and mixed m. p. 253° (effervescence) was confirmed by infrared spectroscopy.

Action of Hydrochloric Acid on the Quinolino-derivatives.—(A) *The* 1-*methyl bases* (III and X; R = Me).[2] (*a*) Pure samples of the isomeric monohydrochlorides (VIII; R = Me), deep red crystals, m. p. 240—245° (E.T.) (from ethanol–acetone) (Found: Cl^-, 12·7. Calc. for $C_{17}H_{14}N_2$,HCl: Cl^-, 12·6%) and (IX; R = Me), bright yellow hydrated needles, m. p. 243—245° (decomp.) (E.T., I.T. 230°) (from ethanol) (Found: Cl^-, 11·9. Calc. for $C_{17}H_{14}N_2$,HCl,H_2O: Cl^-, 11·9%), were prepared for infrared examination.

(*b*) Basification of a solution of the pure hydrochloride (IX; R = Me) gave the isomeric

[19] Braunholtz and Mann, *J.*, 1957, 4166.
[20] Mann and Smith, *J.*, 1951, 1898.
[21] Braunholtz and Mann, *J.*, 1952, 3046.
[22] *Idem*, *J.*, 1954, 651.

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orange base (X; R = Me), m. p. 159—160° (E.T.) (lit.,[2] m. p. 155°) (from acetone), with infrared spectrum identical with that recorded earlier.[2] This sample was used for the nuclear magnetic resonance investigation.

(B) *The* 1-*phenyl bases* (III and X; R = Ph). (*a*) A solution of the base (III; R = Ph), when treated with dry hydrogen chloride, precipitated the deep red monohydrochloride [1] (VIII; R = Ph), m. p. 285—290° (E.T.; colour change to yellow-brown before melting) [lit.,[1] m. p. 280° (decomp.)] (from ethanol containing a small quantity of hydrogen chloride) (Found: C, 76·65; H, 5·2; Cl^-, 10·1. Calc. for $C_{22}H_{16}N_2$,HCl: C, 76·7; H, 5·0; Cl^-, 10·3%). Prolonged treatment with hydrogen chloride did not furnish a colourless dihydrochloride (cf. III; R = Me[2]).

(*b*) A suspension of the base (III; R = Ph) in concentrated hydrochloric acid–ethanol (3 : 1 by vol.) was boiled under reflux for 8 hr. in nitrogen, very little colour change occurring in the dark red solution. The mixture when set aside overnight deposited a *monohydrochloride*, plum-coloured plates with a metallic sheen, m. p. 285—290° (E.T., I.T. 275°; colour change to yellow-brown before melting) (Found: Cl^-, 9·95. $C_{22}H_{16}N_2$,HCl,H_2O requires Cl^-, 9·75%). This hydrochloride, which was probably dimorphous with (IX; R = Ph) (see p. 3370), could not be obtained free from traces of its precursor (VIII; R = Ph), which coloured its solutions red-brown; on basification it yielded the crude orange base (X; R = Ph).

(*c*) When the purple solution of the base (III; R = Ph) (300 mg.) in concentrated hydrochloric acid (12 c.c.) containing dioxan (1—2 c.c.) was boiled under reflux for 4 hr., its colour gradually changed to bright yellow, with a greenish fluorescence; on cooling, the solution deposited almost quantitatively the bright yellow *monohydrochloride monohydrate* [2] (IX; R = Ph), m. p. 290—295° (E.T., I.T. 250°) (lit.,[2] 228—230° from room temperature) (from water containing a trace of ethanol) (Found: C, 73·1; H, 5·4; Cl^-, 9·85. Calc. for $C_{22}H_{16}N_2$,HCl,H_2O: C, 72·9; H, 5·25; Cl^-, 9·75%). (The composition of the sample briefly recorded earlier [2] was incorrectly shown as $C_{22}H_{18}N_2$,HCl.) It is noteworthy that both the " isomeric " yellow hydrochlorides (IX; R = Me or Ph) differ from their red precursors (VIII; R = Me or Ph) in the tenacity with which they retain one molecule of water of crystallisation.

(C) *The* 1-*toluene*-p-*sulphonyl base* (III; R = SO_2·C_6H_4Me). (*a*) Treatment of an ethereal solution of the derivative (III; R = SO_2·C_6H_4Me) with dry hydrogen chloride in the usual way afforded the pale yellow monohydrochloride (VIII; R = SO_2·C_6H_4Me), m. p. 180—185°, which was too unstable to be completely purified for analysis.

(*b*) A solution of the base (III; R = SO_2·C_6H_4Me) (30 mg.) in ethanol (1 c.c.) mixed with dilute hydrochloric acid (2 c.c.) was boiled under reflux for 4 hr., and on cooling deposited the yellow crystalline hydrochloride (VIII; R = SO_2·C_6H_4Me) (30 mg.), which was identified by infrared analysis, and on basification yielded the starting material (III; R = SO_2·C_6H_4Me).

(*c*) When the bright yellow solution of the base (III; R = SO_2·C_6H_4Me) (120 mg.) in concentrated hydrochloric acid (5 c.c.) containing a few drops of ethanol was boiled under reflux for 2 hr., the colour changed to deep orange and the solution deposited the bright yellow 1 : 4′-dihydroquinolino(3′ : 2′-3 : 4)quinoline monohydrochloride [2,13] (X; R = H) (75 mg., 89%), m. p. 322—323° (decomp.) (E.T., I.T. 160°) (lit.,[2] m. p. 310—312°), yellow needles (from aqueous ethanol) (Found: Cl^-, 13·2. Calc. for $C_{16}H_{12}N_2$,HCl: Cl^-, 13·2%). The identity of this salt was confirmed by infrared spectroscopy.

(D) *The naphthoquinoline* (XIII; R = H). (*a*) A solution of the base (XIII; R = H) in ether–acetone, when treated with dry hydrogen chloride, afforded the unstable pale yellow hydrochloride, m. p. 223° (decomp.) (lit.,[11] m. p. 226°) (Found: Cl^-, 13·6. Calc. for $C_{17}H_{13}N$,HCl: Cl^-, 13·3%).

(*b*) No colour change occurred when a solution of the base (XIII; R = H) in concentrated hydrochloric acid was boiled under reflux for 6 hr.; the cooled solution furnished the above hydrochloride, which on basification regenerated the base (XIII; R = H), m. p. and mixed m. p. 58—59°, with infrared characteristics identical with those of the authentic material.

1 : 4′-*Dihydro*-1-*phenylquinolino*(3′ : 2′-3 : 4)*quinoline* (X; R = Ph).—A solution of the yellow monohydrochloride (IX; R = Ph) in air-free water was filtered into a dilute solution of sodium carbonate in air-free water, in a nitrogen atmosphere. The orange amorphous precipitate was washed with cold water and dried under a vacuum at room temperature, affording 1 : 4′-*dihydro*-1-*phenylquinolino*(3′ : 2′-3 : 4)*quinoline* (X; R = Ph), m. p. 89—90° (E.T., I.T. 85°) (Found: C, 83·6; H, 5·25; N, 8·9. $C_{22}H_{16}N_2$ requires C, 85·7; H, 5·2; N, 9·1%). The base could not be satisfactorily recrystallised, nor could a satisfactory carbon analysis be

obtained. Molecular-weight determination by the drop-evaporation method [23] ($0{\cdot}67 \times 10^{-2}$M in chloroform) gave values 291, 337 (calc., 308).

The base (X; R = Ph) (50 mg.) when heated at 200—250°/0·01 mm. afforded a clear yellow distillate which solidified, to give the " parent base," 1 : 2-dihydro-1-phenylquinolino(3′ : 2′-3 : 4)quinoline (III; R = Ph) (40 mg., 80%), m. p. 138—140° (from ethanol), undepressed on admixture with the authentic material and having an identical infrared spectrum.

Atmospheric and Permanganate Oxidation of the Bases.—(*a*) An acetone solution of the orange base (X; R = Ph) was treated at room temperature with a cold saturated acetone solution of potassium permanganate in portions, until the initially rapid decolorisation had ceased. The mixture, when set aside for 1 hr., filtered, and concentrated, deposited 1 : 2-dihydro-2-oxo-1-phenylquinolino(3′ : 2′-3 : 4)quinoline (XI; R = Ph) (yield quantitative), m. p. 255—256° (from ethanol), identical (m. p. and mixed m. p. and infrared spectrum) with the authentic material.[1] The same oxoquinoline (XI; R = Ph) was also obtained when benzene solutions of each isomeric base (III and X; R = Ph) were exposed to the atmosphere for 1 week.

(*b*) Neither of the above methods of oxidation affected the quinolino-bases (III; R = $SO_2{\cdot}C_6H_4Me$) and (XIII; R = H), which were recovered almost quantitatively.

We are greatly indebted to Dr. N. Sheppard for his assistance in the determination and interpretation of the nuclear magnetic resonance spectra.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, April 29th*, 1958.]

[23] Müller and Stolten, *Analyt. Chem.*, 1953, **25**, 1103; see also Taylor and Hall, *ibid.*, 1951, **23**, 947.

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683. *The Structure and Properties of Certain Polycyclic Indolo- and Quinolino-derivatives. Part XI.* Derivatives of 4 : 5 : 6 : 7-Tetrahydro-1-methyl-4-oxo-2 : 3-benzazepine.*

By JOHN T. BRAUNHOLTZ and FREDERICK G. MANN.

4 : 5 : 6 : 7-Tetrahydro-1-methyl-4-oxo-2 : 3-benzazepine in its simple reactions resembles 1 : 2 : 3 : 4-tetrahydro-1-methyl-4-oxoquinoline, but its indolo- and quinolino-derivatives differ markedly from those of the oxoquinoline. The Fischer reaction with the phenylhydrazone yields a true indole instead of a ψ-indole: the quinolino-acid obtained by the Pfitzinger reaction does not show the marked resonance and deep colour of the oxoquinoline derivative, and the corresponding base, obtained by decarboxylation of the acid or by direct application of the Friedländer reaction, does not undergo acid-catalysed allylic rearrangement or ready oxidation to a cyclic amide.

WE have investigated the preparation of 4 : 5 : 6 : 7-tetrahydro-1-methyl-4-oxo-2 : 3-benzazepine (I; R = Me) in order to compare the properties of this seven-membered ketoamine and certain of its polycyclic derivatives with those of 1 : 2 : 3 : 4-tetrahydro-1-methyl-4-oxoquinoline (II) and its corresponding derivatives.[1,2]

1-Arylsulphonyl-4 : 5 : 6 : 7-tetrahydro-4-oxo-2 : 3-benzazepines (*e.g.*, I; R = SO_2Ph) cannot be prepared by Friedel–Crafts cyclisation of γ-arylsulphonamidobutyryl chlorides (*e.g.*, III; R = SO_2Ph),[3,4,5] although the corresponding propionyl chlorides readily give the six-membered derivatives (as II).[6] Compounds such as (I; R = $SO_2{\cdot}C_6H_4Me$-*p*)

* Part X, preceding paper.

[1] Allison, Braunholtz, and Mann, *J.*, 1954, 403.
[2] Braunholtz and Mann, *J.*, 1955, 381.
[3] Astill and Boekelheide, *J. Amer. Chem. Soc.*, 1955, **77**, 4079.
[4] Proctor and Thomson, *J.*, 1957, 2302.
[5] Braunholtz and Mann, *J.*, 1957, 4174.
[6] Clemo and Perkin, *J.*, 1924, **125**, 1608; cf. also Johnson, Woroch, and Buell, *J. Amer. Chem. Soc.*, 1949, **71**, 1901.

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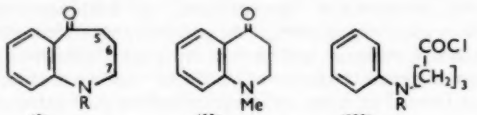
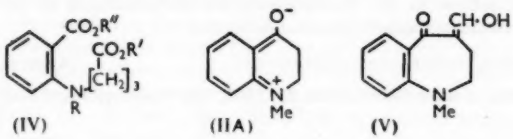
have, however, recently been obtained by Proctor and Thomson [7] by a Dieckmann-type cyclisation, using intermediates such as (IV; R = $SO_2{\cdot}C_6H_4Me$, R′ = R″ = alkyl), and



(I) (II) (III)

the 1-methyl derivative (I; R = Me) has similarly been obtained by Astill and Boekelheide [3] by cyclisation of the diester (IV; R = R′ = R″ = Me), followed by hydrolysis and decarboxylation. We have found that Dieckmann cyclisation of the diester (IV; R = R″ = Me, R′ = Et) under various conditions also gives the 1-methyl derivative (I; R = Me) in *ca.* 50% yield, and have briefly recorded that this compound shows both ketonic and basic properties,[8] contrary to earlier statements.[3]



(IV) (IIA) (V)

The infrared spectrum of this keto-amine is normal and resembles that of the quinolone (II), showing absorption bands [9] due to ≻NMe at 2820 cm.$^{-1}$ and to C=O at 1665 cm.$^{-1}$, with weak absorption at 3480 cm.$^{-1}$ (broad) possibly due to an enolic hydroxyl group; the corresponding bands in the spectrum of the keto-amine (II) are at 2835, 1677, and 3580 (broad) cm.$^{-1}$ respectively.

The ultraviolet spectra of the keto-amines (I; R = Me) and (II) are also closely similar (Fig. 1); the relative position of the long-wavelength absorption maxima suggests, however, that there is in the former compound slightly less interaction between the nitrogen atom and the carbonyl group, of type (IIA).[10] * This is probably due to loss of coplanarity caused by the steric requirements of the saturated seven-membered ring.[11]

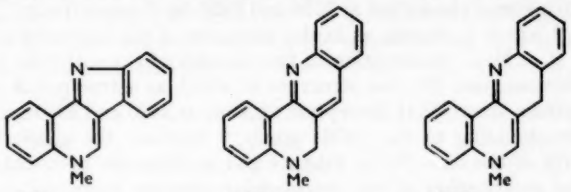
The keto-amine (I; R = Me), in conformity with its spectroscopic similarity to (II), shows normal ketonic reactivity towards phenylhydrazine, 2 : 4-dinitrophenylhydrazine, and semicarbazide. Our efforts to condense the 5-methylene group of the keto-amine with *p*-dimethylaminobenzaldehyde and with *p*-nitrosodimethylaniline have failed, in contrast to the results obtained [13] with the oxoquinoline (II); Astill and Boekelheide [3] have, however, introduced an exocyclic double bond at the 5-position by conversion of the ketone (I; R = Me) into the formyl derivative (V). The basic strength of the keto-amine (I; R = Me), although low, is greater than that of the oxoquinoline (II), for the keto-amine forms a colourless hydrochloride which can be recrystallised from ethanol; in the infrared spectrum of this salt, the ≻NMe absorption band of its parent is absent, but the $\geqslant NH^+$ band is present at 2190 cm.$^{-1}$ and the C=O band at 1685 cm.$^{-1}$, close to its position in the 1-acyltetrahydro-4-oxoquinolines.[10]

The tetrahydro-4-oxoquinolines (*e.g.*, II) are converted by the Fischer and the

* In ref. 10 we misquoted the position of the long-wavelength absorption band of β-tetralone, which should be at 292 mμ (ε 1710) (Fig. 1).

[7] Proctor and Thomson, *J.*, 1957, 2312.
[8] Braunholtz and Mann, *Chem. and Ind.*, 1957, 266.
[9] Braunholtz, Ebsworth, Mann, and Sheppard, *J.*, 1958, 2780.
[10] Braunholtz and Mann, *J.*, 1957, 4166.
[11] Hedden and Brown, *J. Amer. Chem. Soc.*, 1953, **75**, 3744.
[13] Biquard, *Bull. Soc. chim. France*, 1941, **8**, 55.
[13] Ittyerah and Mann, *J.*, 1958, 467.

Pfitzinger (or Friedländer) reaction respectively into ψ-indolo- (*e.g.*, VI) and quinolino- (*e.g.*, VII and VIII) derivatives, which have been extensively investigated.[2,14] 4 : 5 : 6 : 7-Tetrahydro-1-methyl-4-oxo-2 : 3-benzazepine (I; R = Me) is a particularly interesting



(VI) (VII) (VIII)

compound for an extension of these reactions; the mechanisms suggested,[2,14] on the basis of earlier work, to account for the formation of ψ-indoles rather than normal indoles, and for the allylic interconversion (VII ⇌ VIII), are not applicable to the corresponding

FIG. 1. FIG. 2.

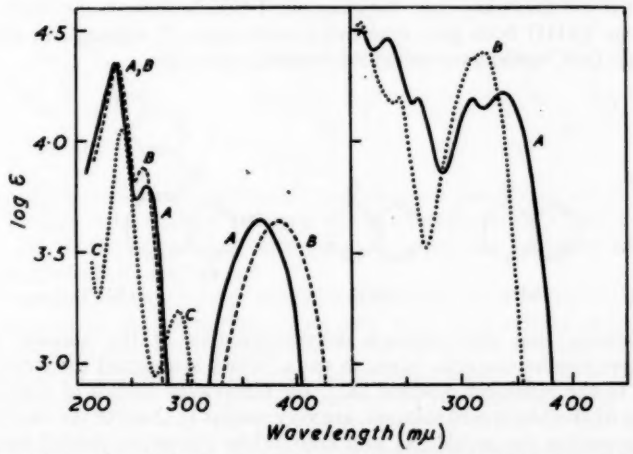
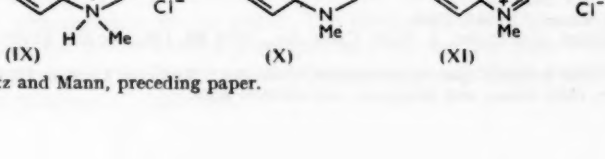


FIG. 1. *Ultraviolet spectra of ethanolic solutions of* (*A*) 4 : 5 : 6 : 7-*tetrahydro*-1-*methyl*-4-*oxo*-2 : 3-*benzazepine* (I; R = Me), (*B*) 1 : 2 : 3 : 4-*tetrahydro*-1-*methyl*-4-*oxoquinoline* (II), *and* (*C*) β-*tetralone* (*see also Biquard* [12]). *Curves* (*A*) *and* (*B*) *have minima at* 294 mμ (log ε 2·556) *and* 288 mμ (log ε 1·740) *respectively, which are not shown.*

FIG. 2. *Ultraviolet spectra of* 6 : 7-*dihydro*-1-*methyl*-2 : 3-*benzindolo*(2′ : 3′-4 : 5)*azepine* (X), (*A*) *in ethanol,* (*B*) *in* 1 : 1 *ethanol–*N*-hydrochloric acid.*

derivatives of the benzazepine system (I; R = Me). The results described below now give strong support for these mechanisms.

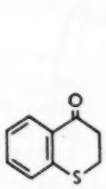


(IX) (X) (XI)

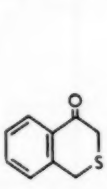
[14] Braunholtz and Mann, preceding paper.

When a solution of the syrupy phenylhydrazone of the oxobenzazepine (I; R = Me) in ethanol saturated with hydrogen chloride is boiled under reflux, the stable colourless monohydrochloride (IX) is obtained in high yield. The indole $>$NH group and the $\geqslant$NH$^+$ group give rise to infrared absorption at 3210 and 2420 cm.$^{-1}$ respectively; $>$NMe absorption in the 2800 cm.$^{-1}$ region is absent, as in the spectrum of the hydrochloride of the parent keto-amine (I; R = Me). Basification of the solution of the salt (IX) yields the cream-coloured indolobenzazepine (X), the structure of which as a true indole is beyond doubt. Its infrared spectrum shows $>$NH absorption maxima at 3420 and 3380 cm.$^{-1}$ and a shoulder (2800 cm.$^{-1}$) corresponding to the $>$NMe group; [9] further, the similarity between the ultraviolet spectra of the base (X) in ethanol and in ethanolic hydrochloric acid (Fig. 2) accords with the protonation of the benzazepine-nitrogen atom rather than that of a ψ-indole, such as (VI), where a marked hypsochromic shift occurs.[2]

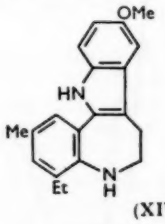
It is thus clear that when the driving force of aromatisation is excluded, the ready abnormal Fischer reaction, described in earlier papers in this series,[2,15] leading to salts (*e.g.*, XI) of ψ-indoles such as (VI), is replaced by normal indolisation. Conjugation of the nitrogen atom of the keto-amine with the potential indolo-nitrogen atom, as in (I; R = Me) and in (II), is, therefore, not a sufficient factor alone for ψ-indole formation, although we believe that it is a necessary one; for example, 1-thiochroman-4-one (XII) and 2-thio-*iso*chroman-4-one (XIII) both give true indolo-derivatives,[16] although in each case the salt of a ψ-indolo-form would have enhanced aromatic character.



(XII)



(XIII)



(XIV)

It is noteworthy that the selenium dehydrogenation of the alkaloid ibogaine is reported [17] to give two heterocyclic bases, to one of which is assigned the structure (XIV), closely related to the indolobenzazepine (X); the ultraviolet spectra of this base (XIV), in ethanolic and hydrochloric acid solution, are very similar to those of the base (X) (Fig. 2).

Attempts to oxidise the indole (X) to a keto-indole derivative yielded mixtures from which pure products could not be isolated; unsuccessful attempts have also been made to dehydrogenate the saturated 6 : 7-linkage, by reagents such as palladium–charcoal or chloranil.

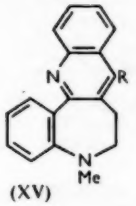
The oxobenzazepine (I; R = Me) reacts with alkaline isatin similarly to the oxoquinoline (IV), giving 6 : 7-dihydro-1-methyl-2 : 3-benzoquinolino(2′ : 3′-4 : 5)azepine-4′-carboxylic acid (XV; R = CO_2H) in moderate yield. This acid, in contrast to the scarlet quinolino-acid [2] (XVII), is pale yellow, melts without immediate effervescence and sublimes unchanged at very low pressures; a slow decarboxylation can be effected at *ca.* 300°/15 mm. These indications that the acid is not zwitterionic (as XVI; R = CO_2^-) are supported by spectroscopic evidence:

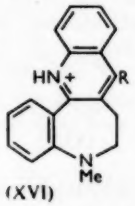
(*a*) The infrared spectrum of the acid (XV; R = CO_2H) does not contain the dominant pair of absorption bands in the regions 1610—1550 and 1400—1300 cm.$^{-1}$ which are characteristic of the carboxylate ion,[18] but resembles that [19] of cinchoninic acid (XVIII) and of

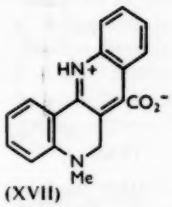
[15] Mann, *J.*, 1949, 2816.
[16] Kiang and Mann, *J.*, 1957, 1909.
[17] Bartlett, Dickel, and Taylor, *J. Amer. Chem. Soc.*, 1958, **80**, 126; see also Taylor, *ibid.*, 1957, **79**, 3298.
[18] Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 1956, p. 149.
[19] Braunholtz, Hall, Mann, and Sheppard, unpublished work.

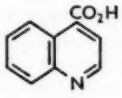
certain other related quinoline-4-carboxylic acids (see preceding paper). Three rather ill-defined regions of absorption are centred at 2450, 1950, and 1700 cm.$^{-1}$, and probably arise from strongly hydrogen-bonded hydroxyl groups.

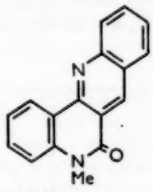
(*b*) The ultraviolet spectra of the acid (XV; R = CO_2H) in neutral and alkaline media are shown in Fig. 3. The similarity between the spectra of the acid and its anion (XV; R = CO_2^-) strongly suggests that the acid does not have the zwitterion structure (XVI;

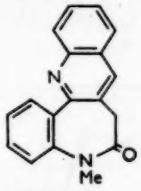

(XV)


(XVI)


(XVII)


(XVIII)


(XIX)


(XX)

R = CO_2^-), which would have additional resonance not possible in the anion (XV; R = CO_2^-). It is noteworthy that the spectrum of the quinolino-acid (XVII), derived from the keto-amine (II), on the other hand, undergoes a very marked hypsochromic shift on passing from neutral to alkaline solution.[2]

These properties (*a*) and (*b*) differ markedly from those of the acid (XVII); it is probable that the formation of the zwitterion occurs only when favoured by additional resonance stabilisation, which apparently cannot occur in the non-planar seven-membered ring.

The Friedländer reaction [14,20] between the oxobenzazepine (I; R = Me) and *o*-aminobenzaldehyde readily gives 6 : 7-dihydro-1-methyl-2 : 3-benzoquinolino(2′ : 3′-4 : 5)azepine (XV; R = H), identical with the product of decarboxylation of the acid (XV; R = CO_2H). The relationship of the base to the analogous quinolino-derivative (VII) may be summarised:

(*a*) The base (XV; R = H) sublimes unchanged; it forms fine cream-coloured needles, whereas the analogous quinolinoquinoline (VII) is intensely yellow. The formulation of the base (XV; R = H) as a true quinoline derivative is supported by the infrared spectrum, which shows the characteristic trio of absorption bands at 1617 (w), 1598 (m), and 1572 cm.$^{-1}$ (w), which have been observed with compounds of type (VII) but not with the allylic isomers (as VIII) (see preceding paper). The expected >NMe absorption band [9] at 2810 cm.$^{-1}$ is also observed.

(*b*) The base (XV; R = H) is unchanged after exposure to the atmosphere in benzene solution for a week, or in the solid state for several weeks, and is not appreciably affected by a cold saturated solution of potassium permanganate. This stability is in marked contrast to that of the bases (VII) and (VIII), which in similar circumstances oxidise readily to the cyclic amide (XIX).

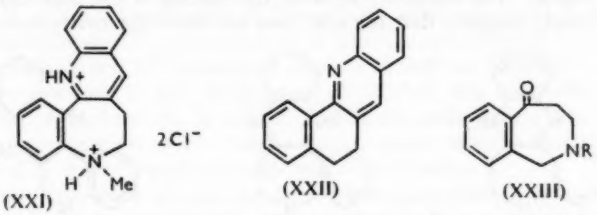
The oxo-derivative (XX) is obtained only when the base (XV; R = H) is boiled in acetone with permanganate for an hour. The disappearance of the *N*-methyl infrared absorption band, the lack of ketonic properties and the very low basic strength show that this oxidation product is the 7-oxo- and not the 6-oxo-isomer, which should be ketonic and

[20] Mann and Wilkinson, *J.*, 1957, 3336.

XUM

should absorb in the 2800 cm.$^{-1}$ region. Infrared absorption due to the carbonyl group occurs at 1660 cm.$^{-1}$, very close to that [2] in the 2-oxoquinolinoquinoline (XIX) (1656 cm.$^{-1}$).

(*c*) Treatment of an acetone solution of the benzoquinolinoazepine with dry hydrogen chloride readily affords either an orange monohydrochloride having the cation (XVI; R = H), or a rather unstable colourless dihydrochloride (XXI), according to the quantity of gas employed. The NMe absorption band is present at 2807 cm.$^{-1}$ in the infrared spectrum of the first salt (XVI; R = H), but is absent from that of the second (XXI).



(XXI) (XXII) (XXIII)

FIG. 3. FIG. 4.

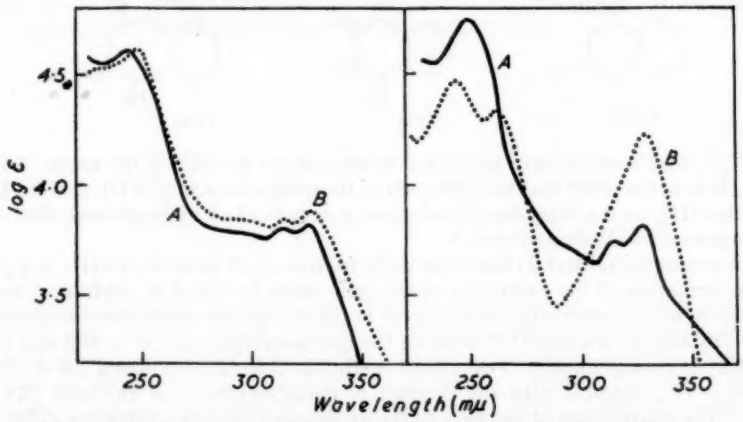


FIG. 3. *Ultraviolet spectra of* 6 : 7-*dihydro*-1-*methyl*-2 : 3-*benzoquinolino*(2′ : 3′-4 : 5)*azepine*-4′-*carboxylic acid* (XV; R = CO_2H), (*A*) *in* 0·1N-NaOH, (*B*) *in ethanol.*

FIG. 4. *Ultraviolet spectra of* 6 : 7-*dihydro*-1-*methyl*-2 : 3-*benzoquinolino*(2′ : 3′-4 : 5)*azepine* (XV; R = H), (*A*) *in ethanol*, (*B*) *in* 1 : 1 *ethanol–*N*-hydrochloric acid.*

This behaviour is similar to that of the corresponding quinolinoquinoline (VII); the ultraviolet spectra of the base (XV; R = H) in neutral and acid solution (Fig. 4) show, however, that the bathochromic shift accompanying salt formation is much less marked with (XV; R = H) than with (VII),[2] and the long-wave absorption intensities are much lower. This is presumably due to the diminished importance of structures in which the positive charge on the 1′-nitrogen atom is borne by the azepine-nitrogen. The observed small shift may in fact be due to contributions of a different type altogether, since an analogous displacement, to longer wavelength, of less than 20 mμ, accompanied by a marked increase in the intensity of absorption, has been found to accompany salt formation in the case of 3 : 4-dihydronaphtho(1′ : 2′-2 : 3)quinoline (XXII) (see preceding paper) and certain related bases in which "classical" cyanine-type resonance is impossible or improbable.

(*d*) The benzoquinolinoazepine (XV; R = H) differs strikingly from the quinolinoquinoline (VII) in its behaviour in hot hydrochloric acid. Although the latter base is thus

rapidly converted into the hydrochloride of the isomeric compound (VIII),[2] the azepine derivative does not undergo rearrangement even on prolonged boiling in concentrated acid, and this treatment yields only the unchanged monohydrochloride (XVI; R = H) and thence the original base (XV; R = H).

The marked differences in behaviour between the derivatives of the ketones (I; R = Me) and (II), brought about solely by the insertion of one additional methylene group into the keto-amine ring of the compound (II), are particularly interesting in connection with the structural features required to facilitate the allylic transformation (*e.g.*, VII ⇌ VIII): these differences emphasise that this allylic system should be directly joined to an atom readily protonated,[2,14] for the interposition of one " insulating " methylene group is sufficient to destroy the activating effect of such a basic centre. It is hoped later to describe indolo- and quinolino-derivatives of an isomeric keto-amine of type (XXIII).

Experimental

Ethyl γ-Bromobutyrate (cf. ref. 4).—Dry hydrogen bromide was bubbled into absolute ethanol (500 c.c.) at 0° until 100 g. had been absorbed. γ-Butyrolactone (67 g.) was added, and the mixture was boiled under reflux for 4·5 hr.; fractional distillation under reduced pressure gave the crude ethyl γ-bromobutyrate (100 g., 77%), b. p. 85—87°/14 mm., n_D^{20} 1·451, sufficiently pure for subsequent use.

Attempts to prepare the methyl ester by an analogous procedure were unsuccessful.

Methyl N-(3-*Ethoxycarbonylpropyl*)*anthranilate* (IV; R = H, R′ = Et, R″ = Me) (cf. ref. 3).—Ethyl γ-bromobutyrate (100 g.) and methyl anthranilate (200 g., 2·2 mol.) were heated together at 100° for 12 hr.; the pasty crystalline mass was then shaken with water (400 c.c.) to which an excess of sodium hydrogen carbonate was gradually added. The mixture was extracted with ether, which when dried and distilled yielded (*a*) unchanged methyl anthranilate (150 g.), b. p. 115—120°/0·4 mm., and (*b*) *methyl*-N-(3-*ethoxycarbonylpropyl*)*anthranilate* (IV; R = H, R′ = Et, R″ = Me) (75 g., 85% based on unrecovered methyl anthranilate), b. p. 176—180°/0·07 mm., forming colourless crystals, m. p. 43·5°, from light petroleum (b. p. 40—60°) (Found: C, 63·65; H, 7·5; N, 5·35. $C_{14}H_{19}O_4N$ requires C, 63·4; H, 7·2; N, 5·3%).

A solution of this diester (5 g.) in aqueous ethanol (25 c.c.: 10 c.c.) containing potassium hydroxide (7 g.), when boiled under reflux for 1 hr., cooled, and acidified to pH 6, deposited the colourless microcrystalline *diacid* (IV; R = R′ = R″ = H) (3·9 g., 95%), m. p. 190° (effervescence) (from ethanol) (Found: C, 59·3; H, 5·75; N, 6·5. $C_{11}H_{13}O_4N$ requires C, 59·2; H, 5·85; N, 6·3%).

Methyl N-*Benzoyl*-N-(3-*ethoxycarbonylpropyl*)*anthranilate* (IV; R = Bz, R′ = Et, R″ = Me).—A solution of the diester (IV; R = H, R′ = Et, R″ = Me) (5 g.) in dry pyridine (20 c.c.) was treated with benzoyl chloride (4·2 g., 1·6 mols.) gradually with shaking and cooling. The pasty mixture was then heated at 50° for 1 hr., cooled, and poured into water (300 c.c.). The heavy oil which separated was collected, washed with water by decantation, and fractionally distilled, giving an almost quantitative yield of *methyl* N-*benzoyl*-N-(3-*ethoxycarbonylpropyl*)-*anthranilate* (IV; R = Bz, R′ = Et, R″ = Me), b. p. 215—225°/0·05 mm. (Found: C, 68·0; H, 6·6; N, 3·85. $C_{21}H_{23}O_5N$ requires C, 68·3; H, 6·3; N, 3·8%); the ester solidified when set aside for 3 months, and then formed colourless needles, m. p. 46°, after crystallisation from ether–light petroleum (b. p. 40—60°).

This diester (1 g.) was quantitatively hydrolysed by boiling it in 50% aqueous ethanol (20 c.c.) containing potassium hydroxide (2 g.) for 45 min.; the cold mixture on acidification gave N-*benzoyl*-N-(3-*carboxypropyl*)*anthranilic acid* (IV; R = Bz, R′ = R″ = H), m. p. 175° (from aqueous ethanol) (Found: C, 66·15; H, 5·3; N, 4·35. $C_{18}H_{17}O_5N$ requires C, 66·1; H, 5·25; N, 4·3%).

Unsuccessful attempts to form the seven-membered ring of the benzazepine system (*e.g.*, I) were made as follows: (*a*) The dicarboxylic acid (IV; R = R′ = R″ = H) was treated with acetic anhydride and potassium acetate under a variety of conditions.[21] Black amorphous solids were the only products isolated. (*b*) The diester (IV; R = Bz, R′ = Et, R″ = Me) in xylene solution, when boiled under reflux with sodium for 9 hr. and then worked up in the usual way (cf. ref. 7), gave no ketonic product.

[21] Uhle, *J. Amer. Chem. Soc.*, 1949, **71**, 761; see also Bekhli, *Doklady Akad. Nauk S.S.S.R.*, 1955, **101**, 679; *Chem. Abs.*, 1956, **50**, 3441ᵉ.

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Methyl N-(3-*Ethoxycarbonylpropyl*)-N-*methylanthranilate* (IV; R = R″ = Me, R′ = Et) (cf. ref. 3).—The secondary amine (IV; R = H, R′ = Et, R″ = Me) (30 g.) and methyl iodide (45 g., 2·8 mol.) were heated together at 90° for 4 hr. in a stainless-steel autoclave. The cold product was added to a mixture of water (100 c.c.) and ether (50 c.c.) and treated with an excess of sodium hydrogen carbonate. The mixture was extracted with ether (400 c.c., portionwise), which was dried and evaporated. Fractional distillation gave a very small fore-run, b. p. 80—115°/0·01 mm., and then the *methyl* N-(3-*ethoxycarbonylpropyl*)-N-*methylanthranilate* (IV; R = R″ = Me, R′ = Et), b. p. 127—133°/0·01 mm. (18 g., 57%); redistillation gave the pure amine, b. p. 139°/0·03 mm. (Found: C, 64·8; H, 7·75; N, 5·25. $C_{15}H_{21}O_4N$ requires C, 64·5; H, 7·6; N, 5·0%).

4 : 5 : 6 : 7-*Tetrahydro*-1-*methyl*-4-*oxo*-2 : 3-*benzazepine* (I; R = Me).—In a typical Dieckmann cyclisation, a solution of the diester (IV; R = R″ = Me, R′ = Et) (6 g.) in dry xylene (35 c.c.) was added during 45 min. to a supension of " molecular " sodium (1 g., 2 g.-atoms) in vigorously stirred, boiling xylene (120 c.c.) under a slow stream of nitrogen, the boiling being then continued with stirring for 7—12 hr. The cold mixture was treated with sufficient methanol to decompose the excess of sodium. The xylene solution was extracted with 6N-hydrochloric acid (3 × 40 c.c.), and the aqueous extract was boiled under reflux in nitrogen for 45 min.; the mixture was cooled, treated with an excess of sodium hydrogen carbonate, and extracted with ether. Fractional distillation of the dried extract under nitrogen gave 4 : 5 : 6 : 7-tetrahydro-1-methyl-4-oxo-2 : 3-benzazepine (I; R = Me) (1·8 g., 48%), b. p. 112°/0·2 mm. (Found: N, 8·25. Calc. for $C_{11}H_{13}ON$: N, 8·0%) (lit.,[3] b. p. 112°/0·07 mm.). The pale yellow liquid ketone did not crystallise; it was stable for several weeks under normal conditions.

When the above procedure was repeated, with toluene in place of xylene, a yield of *ca.* 42% was obtained; when 1 g.-atom of sodium was used, in xylene containing a trace of methanol,[22] with heating under reflux for 10 hr., the yield was 40%. The Dieckmann reaction employing sodium in anhydrous benzene containing a trace of methanol gave a 27% yield, and the use of sodium hydride in dry benzene gave only traces of ketonic material. Repetition of the procedure of Astill and Boekelheide,[3] with boiling dry toluene with potassium *tert.*-butoxide as catalyst, gave the same yield (48%) as in the above experiment.

Derivatives of the Benzazepine (I; R = Me).—(*a*) A solution of the ketone (I; R = Me) (0·5 g.) in ethanol (5 c.c.) containing water (2 c.c.) was treated with semicarbazide hydrochloride (0·35 g.) and sodium acetate; the solution was boiled under reflux in nitrogen for 2 hr. and on cooling deposited 4 : 5 : 6 : 7-*tetrahydro*-1-*methyl*-4-*oxo*-2 : 3-*benzazepine semicarbazone* (0·5 g., 75%), colourless platelets, m. p. 198° (from ethanol) (Found: C, 61·8; H, 6·8; N, 24·4%; *M*, ebullioscopic in ethanol, 244. $C_{12}H_{16}ON_4$ requires C, 62·0; H, 6·95; N, 24·1%; *M*, 232). (*b*) An ethanolic solution of the ketone (I; R = Me) when briefly warmed with a solution of 2 : 4-dinitrophenylhydrazine in ethanolic hydrochloric acid, deposited the stable orange microcrystalline 2 : 4-*dinitrophenylhydrazone*, m. p. 202—203° (Found: N, 19·85. $C_{17}H_{17}O_4N_5$ requires N, 19·6%). (*c*) The phenylhydrazone of the ketone (I; R = Me), prepared in the usual way, formed a viscous syrup which did not crystallise. (*d*) Treatment of an acetone–ether solution of the base (I; R = Me) with dry hydrogen chloride precipitated the colourless *hydrochloride*, m. p. 160—161° (decomp.) after crystallisation from ethanol (Found: C, 62·4; H, 6·6; N, 6·45; Cl, 17·0. $C_{11}H_{13}ON$,HCl requires C, 62·4; H, 6·65; N, 6·6; Cl, 16·75%). (*e*) The picrate was precipitated from aqueous-ethanolic solution by aqueous picric acid but has not been obtained pure.

Reactions of the 5-*Methylene Group*.—All attempts to isolate crystalline products of condensation between the 5-methylene group of the ketone (I; R = Me) and *p*-dimethylaminobenzaldehyde or *p*-nitrosodimethylaniline [23] have failed: the former reagent gave no reaction, and the latter gave intractable tars.

6 : 7-*Dihydro*-1-*methyl*-2 : 3-*benzindolo*(2′ : 3′-4 : 5)*azepine* (X).—A solution of the syrupy phenylhydrazone (from 1·4 g. of ketone) in a mixture of saturated ethanolic hydrogen chloride (50 c.c.) and ethanol (10 c.c.) was boiled under reflux for 8 hr. The deep orange solution became first ruby-red, then slowly yellow-brown while a colourless solid separated. The solution was cooled to 0° for 2 hr., and the solid deposit then collected, washed with cold water, and recrystallised from ethanol containing a trace of water, yielding 6 : 7-*dihydro*-1-*methyl*-2 : 3-*benzindolo*-(2′ : 3′-4 : 5)*azepine hydrochloride* (IX) (2·1 g., 92%), m. p. 235° (effervescence) (Found: C,

[22] Openshaw and Robinson, *J.*, 1946, 912.

71·65; H, 6·25; N, 9·95; Cl, 12·3. $C_{17}H_{14}N_2$,HCl requires C, 72·0; H, 6·0; N, 9·85; Cl, 12·5%).

An aqueous-ethanolic solution of the hydrochloride (IX), when basified with 10% aqueous sodium hydroxide, yielded the *indole* (X), which formed cream-coloured needles, m. p. 119°, from aqueous ethanol in which it formed a colourless solution with a vivid violet fluorescence (Found: C, 82·2; H, 6·9; N, 11·2. $C_{17}H_{14}N_2$ requires C, 82·2; H, 6·5; N, 11·3%).

The indole (X) is completely stable when exposed to the atmosphere; a slow and partial oxidation apparently occurs in hot acetone–permanganate, but no pure derivative has been isolated.

6 : 7-*Dihydro*-1-*methyl*-2 : 3-*benzoquinolino*(2′ : 3′-4 : 5)*azepine*-4′-*carboxylic Acid* (XV; R = CO_2H).—Isatin (1·4 g., 1·2 mols.) and potassium hydroxide (1·7 g., 3·8 mols., in 5 c.c. of water) were added to a solution of the ketone (I; R = Me) (1·4 g.) in ethanol (10 c.c.) which was then boiled under reflux for 10 hr. in a nitrogen atmosphere, cooled, and filtered into an excess of a 10% solution of acetic acid in water. The crude yellow precipitate, when collected and recrystallised from dioxan, yielded **6 : 7-*dihydro*-1-*methyl*-2 : 3-*benzoquinolino*(2′ : 3′-4 : 5)-*azepine*-4′-*carboxylic acid*** (XV; R = CO_2H) (0·75 g., 31%), a pale yellow microcrystalline powder, m. p. 295° (slow effervescence, in evacuated tube, immersion temp. 260°) (Found: C, 74·55; H, 5·6; N, 9·1. $C_{19}H_{14}O_2N_2$ requires C, 74·95; H, 5·3; N, 9·2%).

6 : 7-*Dihydro*-1-*methyl*-2 : 3-*benzoquinolino*(2′ : 3′-4 : 5)*azepine* (XV; R = H).—(A) *By the Friedländer reaction.* A solution of the ketone (I; R = Me) (0·7 g.) in warm ethanol (10 c.c.) was treated with *o*-aminobenzaldehyde [20] (0·5 g., 1 mol.) and aqueous 10% sodium hydroxide (0·2 c.c.), and set aside at room temperature under nitrogen for 1 week. The mixture on dilution with water deposited the crystalline **6 : 7-*dihydro*-1-*methyl*-2 : 3-*benzoquinolino*(2′ : 3′-4 : 5)*azepine*** (XV; R = H) (0·8 g., 75%), colourless needles, m. p. 127° (from aqueous ethanol) (Found: C, 82·9; H, 6·3; N, 10·85. $C_{18}H_{16}N_2$ requires C, 83·0; H, 6·2; N, 10·8%). The base distils smoothly in the sublimation tube at *ca.* 300°/15 mm. without change (shown by m. p. and infrared spectrum).

(B) *By decarboxylation of the quinolino-acid* (XV; R = CO_2H). (*a*) The acid when heated in a tube at 0·002 mm. sublimed at 250—310° without residue. The yellow crystalline sublimate had m. p. and mixed m. p. 285—290°, and its infrared spectrum was identical with that of the original material.

(*b*) In a similar experiment at 15 mm. a clear viscous orange-yellow distillate was obtained at *ca.* 300°, and solidified to a glass on cooling. This product was shown, by infrared and chromatographic analysis to be the almost pure quinolino-base (XV; R = H) contaminated with traces of the acid (XV; R = CO_2H) which were readily removed by recrystallisation from aqueous ethanol.

Derivatives of the Quinolino-base (XV; R = H).—(*a*) The base reacted with boiling methyl iodide, to give the unstable *methiodide*, an orange microcrystalline powder, m. p. 210—211° (effervescence) (from acetone containing a trace of methanol) (Found: N, 7·05. $C_{19}H_{19}N_2I$ requires N, 7·0%).

(*b*) A dry ethereal solution of the pure base (XV; R = H) on cautious treatment with a slow stream of dry hydrogen chloride deposited the bright orange *monohydrochloride* (cation as XVI; R = H), m. p. 194—196° (Found: Cl^-, 12·3. $C_{18}H_{16}N_2$,HCl requires Cl^-, 12·0%). This salt could not be recrystallised satisfactorily; it dissolved readily in cold ethanol to give a stable deep orange solution, decolorised by additional hydrogen chloride (see below), whereas its solution in water slowly deposited the free base.

(*c*) A solution of the pure base in dry acetone, when treated with an excess of dry hydrogen chloride, became first orange, then colourless, and deposited the colourless *dihydrochloride* (XXI), m. p. 200—205° (giving a deep red liquid, and darkening and decomposing progressively before melting) after being washed with warm acetone (Found: Cl^-, 20·5. $C_{18}H_{16}N_2$,2HCl requires C, 21·0%). This salt was unstable; it gave orange solutions (*e.g.*, in ethanol), and became pink when exposed to the atmosphere or (rapidly) when heated.

(*d*) Several attempts were made to effect the acid-catalysed isomerisation of the base (XV; R = H). The unchanged base or its hydrochloride was recovered almost quantitatively after being boiled in solution in dilute hydrochloric acid (4 hr.), in concentrated hydrochloric acid (6 hr.), or in concentrated hydrochloric acid containing a small quantity of dioxan (6 hr.). Identification in each case was confirmed by infrared spectroscopy.

Permanganate Oxidation of the Base (XV; R = H).—A boiling solution of the

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quinolino-base (XV; R = H) (50 mg.) in acetone (10 c.c.) was treated with an excess of saturated acetone–permanganate (in portions) during 2 hr.; the solution was further boiled under reflux until the purple colour disappeared, then cooled and filtered. The filtrate, when concentrated, filtered again, and cooled, deposited 6 : 7-*dihydro*-1-*methyl*-7-*oxo*-2 : 3-*benzoquinolino*(2′ : 3′-4 : 5)*azepine* (XX) (50 mg., 95%), colourless needles, m.p. 192—193° (from aqueous ethanol) (Found: C, 78·65; H, 5·35; N, 10·45. $C_{18}H_{14}ON_2$ requires C, 78·8; H, 5·15; N, 10·2%). The cyclic amide (XX), which cannot be obtained at room temperature by atmospheric oxidation in benzene solution or by permanganate oxidation in acetone solution, does not form a stable hydrochloride and does not react with 2 : 4-dinitrophenylhydrazine.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, April 29th*, 1958.]

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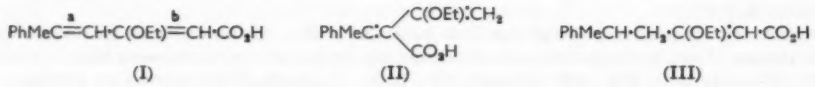
684. *The Reactive Methyl Group of Ethyl β-Ethoxycrotonate.*

By F. M. DEAN, CORNELIUS STEELINK, and JOHN TETAZ.

Base-catalysed condensation of ethyl β-ethoxycrotonate and acetophenone gives β-ethoxy-δ-phenylsorbic acid in two forms geometrically isomeric about the γδ-double bond.

THE preparation of 1 : 3 : 5-triketones is of importance in connection with the acetate theory of biogenesis propounded by Birch *et al.*,[1] but cannot be achieved by Claisen condensations with ethyl acetoacetate because of inactivation of the ester and methyl groups in the enolate. Ethyl β-ethoxycrotonate is free from this drawback but has now been found to react at the active methyl group rather than at the ester group. Thus sodium hydride induced condensation of ethyl β-ethoxycrotonate with acetophenone, giving β-ethoxy-δ-phenylsorbic acid (I) in two isomers, A, m. p. 142°, $\lambda_{max.}$ (in EtOH) 231, 296 mμ (log ε 4·08, 4·20), and B, m. p. 108°, $\lambda_{max.}$ 230, 287 mμ (log ε 3·99, 4·20).

The absence of carbonyl groups was evident from the lack of reaction of either isomer with semicarbazide and similar carbonyl reagents, with sodium borohydride, and with ferric chloride. The carboxyl group was abnormal since it is vinylogous with carbonic acid but was clearly responsible for the very weak acidity (in 50% alcohol, isomer A had pK_a 6·85 and B had pK_a 6·98: benzoic acid has pK_a 5·55) and for the broad infrared absorption bands at 3 μ. The conjugated carboxyl group was also responsible for complex and intense absorption bands near 6·5 μ, and for the hypsochromic shift in the ultraviolet spectrum produced by alkaline alcohol in which compound A had $\lambda_{max.}$ 290 mμ (log ε 4·22) and B had $\lambda_{max.}$ 281 mμ (log ε 4·22).



(I) (II) (III)

The presence of a β-ethoxyacrylic acid system was disclosed by the stability of both isomers A and B to alkali, as opposed to their ready hydrolysis by cold dilute acids which gave oils initially giving a bluish-red ferric reaction but owing to decarboxylation affording the semicarbazone [2] of 4-phenylpent-3-en-2-one.

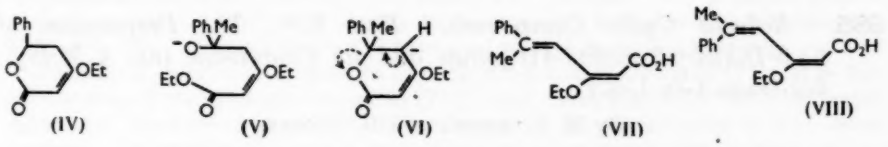
Care was taken to exclude structure (II) because this type of condensation product can be important and sometimes dominant.[3] Hydrogenation of isomers A and B gave the same dihydro-derivative (III), retaining a weakly acidic carboxyl group (pK_a in 50% alcohol, 7·02), having $\lambda_{max.}$ 238 mμ (log ε 4·11) similar to that of β-ethoxycrotonic acid [4] and yielding, by acid hydrolysis, 4-phenylpentan-2-one (carbonyl absorption at 1724 cm.$^{-1}$) characterised as the semicarbazone. Ozonolysis of this dihydro-derivative gave a neutral

[1] Birch, Massey-Westropp, Rickards, and Smith, *J.*, 1958, 360.
[2] Ghate, Kaushal, and Deshapande, *J. Indian Chem. Soc.*, 1950, **27**, 633.
[3] Bohlmann, *Chem. Ber.*, 1957, **90**, 1519.
[4] Russoff, *J. Amer. Chem. Soc.*, 1945, **67**, 677.

oil which on hydrolysis furnished β-phenylbutyric acid identified with authentic material [5] by means of the *S*-benzyl*iso*thiuronium salt, thus excluding structure (II) for either compound A or B.

Because the ultraviolet spectra precluded the existence of either isomer in the form of a lactone (IV), the isomerism must involve either or both the bonds (a) and (b); but it was difficult to define this further because both isomers gave the same dihydro-derivative (III) and 4-phenylpent-3-en-2-one. Since the inversions involved could have arisen either by 1 : 4-addition of hydrogen or by acid-catalysed rearrangement, configurations have been tentatively allocated by indirect means.

Reid and Ruby [6] obtained lactone (IV) from the Reformatsky reaction between benzaldehyde and ethyl γ-bromo-β-ethoxycrotonate and isomerised it with alkali to the corresponding acid [(I) H for Me]: these reactions are of course closely related to those now being discussed. Hydrolysis of β-alkoxyacrylates by the usual methods is difficult because of the reduced carbonyl character of the ester system, and under the conditions employed in this work ethyl β-ethoxycrotonate was hardly affected. Consequently the apparent hydrolysis of the ester group during the formation of acid (I) possibly results from the formation of ion (V) in which extrusion of ethoxide is aided by the stereochemical factor. The resulting lactone still possesses an active methylene group and with sodium hydride would yield the carbanion (VI) and thence the carboxylate without the intervention of hydrolysis.



(IV) (V) (VI) (VII) (VIII)

Because the electronic interaction of ethoxyl and carboxyl in the carboxylate is minimal, inversion at bond (b) would be most improbable, and therefore the above hypothesis requires both isomers to have ethoxyl *trans* to carboxyl. The isomerism is therefore confined to bond (a). Clearly, ring fission in the pyranone (VI) with phenyl in the quasi-equatorial position leads to an acid (I) in which phenyl is *cis* to hydrogen as in (VII), whereas with methyl in the quasiequatorial position ring fission leads to (VIII). The production of but one acid [6] from lactone (IV) is intelligible since in this lactone the form with a quasiequatorial phenyl group must predominate.

The solubilities, melting points, and ultraviolet spectra all indicate that isomer A should be allocated the more nearly "*trans*"-configuration and more highly conjugated structure. Therefore isomer A has structure (VII) and isomer B has structure (VIII).

Experimental

Isomers A and B of β-Ethoxy-δ-phenylsorbic Acid (I).—To sodium hydride (14·4 g.) in ether (1 l.) stirred under nitrogen were added ethyl β-ethoxycrotonate (32 g.) and acetophenone (24 g.) also in ether (200 ml.). After 9 hr. at the b. p. the orange mixture was freed from sodium hydride by water, and the ethereal layer was distilled, giving ethyl β-ethoxycrotonate, b. p. 99°/25 mm. (16 g.). When acidified at 10° by 2N-hydrochloric acid, the aqueous layer gave a solid (10·4 g.), separated by fractional crystallisation from light petroleum (b. p. 60—80°) into a less soluble component, *isomer A*, long needles, m. p. 142° (decomp.) (Found: C, 72·2; H, 7·2; OEt, 20·0. $C_{13}H_{11}O_2$·OEt requires C, 72·3; H, 6·9; OEt, 19·4%), and a more soluble component, *isomer B*, prisms, m. p. 108° (decomp.) (Found: C, 72·1; H, 7·1; OEt, 22·0%).

Hydrolysis of Isomers A and B.—When isomer A or B (1 g.) was shaken for 1 day with 2N-hydrochloric acid (80 ml.) it furnished an oil having a reddish-blue ferric reaction in alcohol and

[5] Lipkin and Stewart, *J. Amer. Chem. Soc.*, 1939, **61**, 3295.
[6] Reid and Ruby, *ibid.*, 1951, **73**, 1054.

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yielding the semicarbazone, m. p. 188° (Found: C, 66·2; H, 6·9; N, 19·1. Calc. for $C_{12}H_{15}ON_3$: C, 66·4; H, 7·0; N, 19·4%), of 4-phenylpent-3-en-2-one identical with an authentic specimen.[2]

3-Ethoxy-5-phenylhex-2-enoic Acid (III).—Isomer A or B (200 mg.) in ethyl acetate (50 ml.) containing palladium–barium sulphate (50 mg.) absorbed hydrogen (22 ml.) in 1½ hr., giving the *hexenoic acid*, which crystallised from light petroleum (b. p. 40—60°) and then aqueous alcohol in needles, m. p. 104—106° (Found: C, 72·0; H, 7·8; OEt, 19·6. $C_{12}H_{13}O_2$·OEt requires C, 71·8; H, 7·7; OEt, 19·2%).

Reactions of Acid (III).—(*a*) The acid (0·6 g.) was shaken with 2N-hydrochloric acid (100 ml.) for 1 day, giving an oil with a wine-red ferric reaction and furnishing the semicarbazone, m. p. 138° (Found: C, 65·2; H, 8·2; N, 19·8. Calc. for $C_{12}H_{17}ON_3$: C, 65·7; H, 7·8; N, 19·2%), of 4-phenylpentan-2-one.[7]

(*b*) The acid (0·3 g.) in ethyl acetate (40 ml.) at −10° was ozonised for 40 min. The residue after removal of the solvent was kept with warm water (25 ml.) and zinc dust. Next day the neutral fraction of the product was hydrolysed by 8% aqueous sodium hydroxide on the steam-bath for 4 hr., giving β-phenylbutyric acid as an oil which supplied the S-*benzylisothiuronium salt* in plates (from water), m. p. 148—149° (Found: C, 65·6; H, 6·3. $C_{18}H_{22}O_2N_2S$ requires C, 65·5; H, 6·7%), identified by the mixed m. p. and infrared methods with a sample prepared from authentic β-phenylbutyric acid.[5]

THE UNIVERSITY OF LIVERPOOL. [*Received, May 14th*, 1958.]

[7] Chiang, *J. Chinese Chem. Soc.* (*Formosa*), 1951, **18**, 65.

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685. *Reduced Cyclic Compounds. Part V.* The Preparation of 5 : 6-Dihydro-3-methyl-4H-pyran and its Conversion into 4-Methylhex-*trans*-4-*en*-1-*ol*.†*

By M. F. ANSELL and B. GADSBY.

The preparation of 5 : 6-dihydro-3-methyl-4*H*-pyran and its conversion, involving ring scission of 3-chlorotetrahydro-2 : 3-dimethylpyran by sodium, into 4-methylhex-*trans*-4-en-1-ol ‡ are described. The configuration of the alcohol is deduced by comparison of its derivatives with those of the 4-methylhept-4-en-1-ols obtained from tiglic and angelic acid, methyl 3-methylpent-*trans*-3-enoate, and *cis*- and *trans*-2-bromobut-2-ene. The mechanism of the ring scission of 3-chlorotetrahydropyrans is discussed.

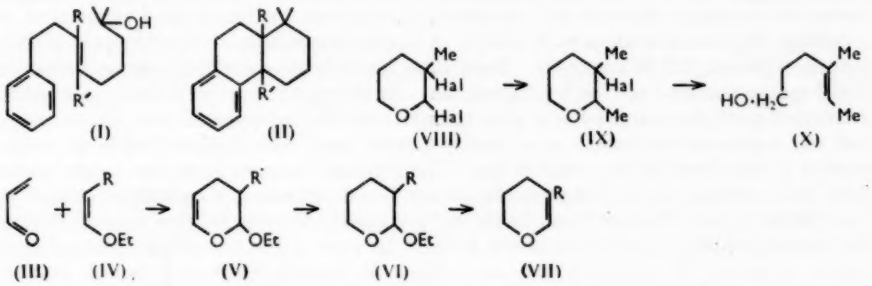
THE use of 2 : 3-dichlorotetrahydropyran in the preparation of the ω-arylolefinic alcohol (I; R = R′ = H) and its cyclodehydration to the hydrocarbon (II; R = R′ = H) has been described.[1] To extend this synthesis to compounds containing an angular methyl group, 5 : 6-dihydro-2- and -3-methyl-4*H*-pyran are required: only the former has been previously reported.[2]

A convenient and unambiguous route to 2 : 3-dihydro-4*H*-pyran is the Diels–Alder reaction of acraldehyde with a vinyl ether,[3] followed by hydrogenation to the 2-alkoxytetrahydropyran and pyrolysis to yield the dihydropyran (III ⟶ VII; R = H). This route is adaptable; 2 : 3-dihydro-4-methyl- and 2 : 3-dihydro-2-methoxy-5-methyl-4*H*-pyran have been prepared from crotonaldehyde and 2-methylacraldehyde respectively.[4,5] We have utilised it for the preparation of 5 : 6-dihydro-3-methyl-4*H*-pyran (VII; R = Me) from acraldehyde (III) and ethyl propenyl ether (IV; R = Me).

* Part IV, *J.*, 1958, 2955.
† Presented in part at the XVIth Internat. Congr. Pure Appl. Chem., Paris, 1957.
‡ The prefix *cis* or *trans* refers to the main chain in accordance with I.U.P.A.C. recommendations (cf. *J.*, 1952, 5059).

[1] Ansell and Selleck, *J.*, 1956, 1238.
[2] Perkin, *J.*, 1887, **51**, 702.
[3] Longley and Emerson, *J. Amer. Chem. Soc.*, 1950, **72**, 3079.
[4] Smith, Norton, and Ballard, *ibid.*, 1951, **73**, 5267.
[5] Parham and Holmquist, *ibid.*, p. 913.

For the catalytic pyrolysis of 1 : 1-diethoxypropane (obtained from ethyl orthoformate and excess of ethylmagnesium bromide [6] rather than excess of orthoformate [7]) into ethyl propenyl ether, both acid [8] and kaolin [9] have been used. We found the latter more convenient. Alumina was unsuitable. Condensation of the propenyl ether with acraldehyde at 180° yields 2-ethoxy-2 : 3-dihydro-3-methyl-4*H*-pyran (V; R = Me) smoothly,



whose structure was confirmed by hydrolysis to 2-methylglutaraldehyde, identified by conversion into 2-methylglutaric acid. Hydrogenation of the ether (V; R = Me) gave 2-ethoxytetrahydro-3-methylpyran (VI) which was pyrolysed over a kaolin catalyst (cf. the preparation of ethyl propenyl ether above) to yield 5 : 6-dihydro-3-methyl-4*H*-pyran (VII; R = Me). Previous workers [4,5] have used an acid catalyst at this stage.

Addition of chlorine or bromine to 5 : 6-dihydro-3-methyl-4*H*-pyran (VII; R = Me), and coupling of the resultant compound (VIII) with methylmagnesium bromide readily yielded the 3-halogenotetrahydro-2 : 3-dimethylpyran (IX) (presumably as a *cis-trans*-mixture). The bromide (IX) lost hydrogen bromide on distillation under reduced pressure giving a dihydro-2 : 3-dimethylpyran isolated in the subsequent stage, but the chloride was stable. Both halogeno-compounds readily underwent ring scission with sodium to yield as the sole product 4-methylhex-*trans*-4-en-1-ol (X) whose structure was confirmed by the formation of acetaldehyde on ozonolysis and the known 4-methylhexan-1-ol [10] on hydrogenation. The evidence for the allocation of the *trans*-configuration to this alcohol is discussed below.

4-Methylhex-4-en-1-ols

Source of alcohol	B. p.°/mm.	n_D^{20}	α-Naphthylurethane, m. p.*	4-Diphenylylurethane, m. p.*
Ring scission	82/16	1·4512	76·5—77°	97—98°
Tiglic acid	82/16	1·4512	76·5—77	97—98
Methyl 3-methylpent-*trans*-3-enoate	79/16	1·4520	75·5—76	—
Angelic acid	80/16	1·4504	73·5—74·5	94—95
2-Bromobut-*trans*-2-ene	78/15	1·4498—1·4506	61—65 †	93—95 †
2-Bromobut-*cis*-2-ene	78·5/15·5	1·4499—1·4507	65—67 †	99·5—101 †

* M. p.s after two recrystallisations except those marked † which are after six recrystallisations.

A possible route to pure *cis*- and *trans*-4-methylhex-4-en-1-ols starts from methyl 3-methylpent-3-enoate which is obtainable [11] stereochemically pure by the Favorski rearrangement of 3 : 4-dibromo-3-methylpentan-2-one. Unfortunately the configuration of this ester, although accepted as *trans* by Wagner [11] and by Loftfield,[12] is not firmly

[6] Wood and Comley, *J. Soc. Chem. Ind.*, 1923, **42**, 430 T.
[7] Kranzfelder and Vogt, *J. Amer. Chem. Soc.*, 1938, **60**, 1714.
[8] Voronkov, *J. Gen. Chem.* (*U.S.S.R.*), 1950, **20**, 2060.
[9] Deschamps, Paty, and Pineau, *Compt. rend.*, 1954, **238**, 2006.
[10] Huston and Agett, *J. Org. Chem.*, 1941, **6**, 123.
[11] Wagner, *J. Amer. Chem. Soc.*, 1949, **71**, 3214.
[12] Loftfield, *ibid.*, 1951, **73**, 4707.

established. The parent acid was assigned the *trans*-configuration by Kon, Linstead, and Wright [13] on the basis of its non-identity with a stereoisomeric acid " provisionally called *cis*." However, the allocation of a *trans*-configuration to this acid is consistent with our own results (see below).

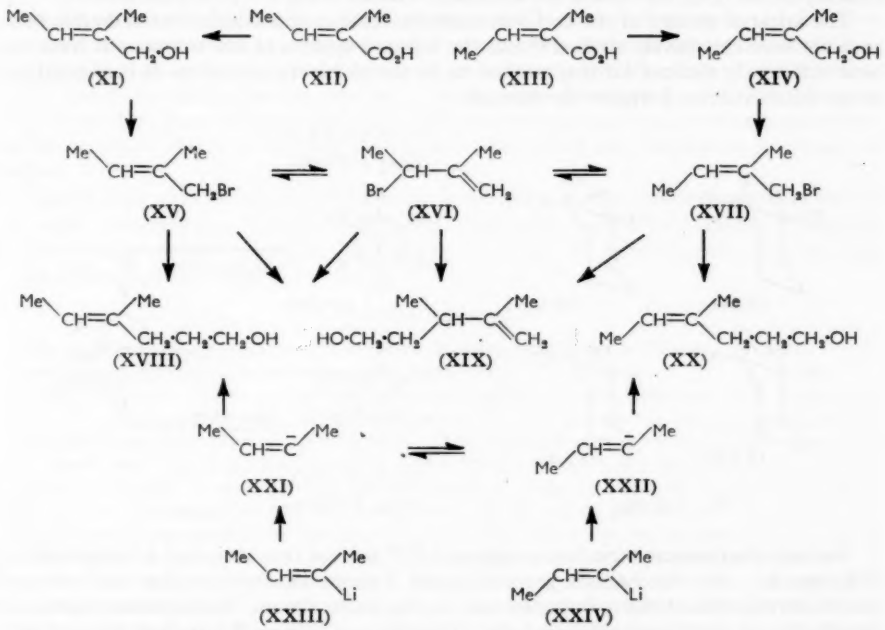
Methyl 3-methylpent-*trans*-3-enoate was reduced to 3-methylpent-*trans*-3-en-1-ol. Conversion of the latter into the *cis*-isomer [14] by the addition of chlorine (*trans*), elimination (*trans*) of hydrogen chloride with propanolic potassium hydroxide, and removal of the resulting vinyl halogen atom with sodium in liquid ammonia, gave 3-methylpent-*cis*-3-en-1-ol as expected, but in low yield. Both these alcohols gave acetaldehyde on ozonolysis, and 3-methylpentan-1-ol [10] on hydrogenation. An attempt to convert the *trans*-alkenol into 1-chloro-3-methylpent-*trans*-2-ene with thionyl chloride and pyridine was unsuccessful,[15] but the toluene-*p*-sulphonate was readily formed and with sodium iodide in acetone yielded 1-iodo-3-methylpent-*trans*-2-ene. The Grignard reagent from this iodide reacted with formaldehyde to give 4-methylhex-*trans*-4-en-1-ol, whose α-naphthylurethane was identical with that obtained from the alcohol prepared in the ring scission, thus establishing the stereochemical homogeneity of the latter. In view of the low yields obtained in the above sequence of reactions the conversion of 3-methylpent-*cis*-3-en-1-ol into the homologous alcohol was not attempted.

An alternative route to *cis*- and *trans*-4-methylhex-4-en-1-ol is from the readily available [16] stereochemically pure tiglic (XII) and angelic acid (XIII) whose configurations are well established.[17] This route necessitates the use of allylic halides as intermediates, and although such compounds have been used successfully in the preparation of authentic *cis*- and *trans*-isomers [18] stereoisomerisation or rearrangement may occur. Tiglic (XII) and angelic acid (XIII) were reduced to the allylic alcohols (XI and XIV) which were then treated with phosphorus tribromide. From both alcohols it is conceivable [19] that essentially the same equilibrium mixture of pentenyl bromides (XV, XVI, and XVII) could be obtained in which, by analogy with the preferential stability of tiglic acid,[20] the primary halide present would be predominantly (XV). While primary allylic halides react with ethyl sodiomalonate by an S_N2 mechanism with retention of configuration, rearrangement may occur by an S_N2' mechanism.[21] Further the secondary halide (XVI) may react by an S_N2' mechanism to yield structurally the same product as is obtained from the primary halide by n S_N2 mechanism. However, this route yields the more thermodynamically stable product [22] which would be expected to be the *trans*-isomer (XVIII). Thus treatment of the pentenyl halides, from either source, with ethyl sodiomalonate followed by hydrolysis, decarboxylation, and reduction, would be expected to give a mixture of the alcohols (XVIII, XIX, and XX) in which the *trans*-isomer (XVIII) would predominate. This result was achieved experimentally. The heptenol mixture derived from tiglic acid yielded 2 : 3-dimethylpent-1-en-5-ol (XIX) [detected by infrared bands at 887 and 1650 cm.$^{-1}$ (=CH_2)] and 4-methylhex-4-en-1-ol (ozonolysis gave acetaldehyde and hydrogenation gave 4-methylhexan-1-ol), the latter identical with the alcohol obtained in the ring scission which has already been shown to be stereochemically pure and which we therefore consider from the above discussion to be *trans*. Fractional distillation of the heptenol mixture derived from angelic acid afforded 2 : 3-dimethylpent-1-en-5-ol (XIX) and 4-methylhex-4-en-1-ol (ozonolysis gave acetaldehyde, and hydrogenation gave 4-methylhexan-1-ol)

[13] Kon, Linstead, and Wright, *J.*, 1934, 599.
[14] Cf. Hoff, Greenlee, and Boord, *J. Amer. Chem. Soc.*, 1951, **73**, 3329.
[15] Cf. Ansell and Brown, *J.*, 1957, 1788.
[16] Buckles and Mock, *J. Org. Chem.*, 1950, **15**, 680.
[17] Korte and Behner, *Chem. Ber.*, 1956, **89**, 2675; Titov, *Zhur. obshchei Khim.*, 1948, **18**, 1467; *Chem. Abs*, 1949, **43**, 2166.
[18] Birch and McAllan, *J.*, 1951, 2556.
[19] Cf. Hatch and Journeay, *J. Amer. Chem. Soc.*, 1953, **75**, 3712.
[20] Buckles, Mock, and Locatell, *Chem. Rev.*, 1955, **55**, 659.
[21] De Wolfe and Young, *ibid.*, 1956, **56**, 753.
[22] Prévost, *Ann. Chim.* (*France*), 1928, **10**, 113; Valette, *ibid.*, 1946, **3**, 644.

which, as judged from the melting points of its derivatives (see Table), was predominantly the *trans*-isomer.

A third route to 4-methylhex-4-en-1-ol is the reaction of 2-lithiobut-2-ene with trimethylene oxide. This chain extension procedure, which has been used with alkyl- and aryl-lithiums and Grignard reagents,[23] has not previously been used with an alkenyllithium. Reaction of the lithio-derivatives (XXIII and XXIV) of *cis*- and *trans*-but-2-ene



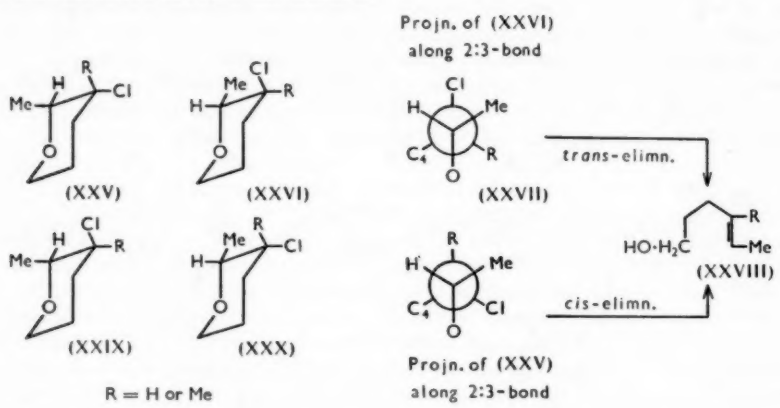
with carbon dioxide has been shown to be predominantly stereospecific,[24] although the retention of configuration is greater with the *trans*-isomer (the *cis*-isomer yields angelic and tiglic acid in the ratio of approximately 3 : 7 whereas with the *trans*-isomer the ratio is approximately 9 : 1). We have found that when either of these alkenyl-lithiums reacts with trimethylene oxide a mixture of *cis*- and *trans*-4-methylhex-4-en-1-ols is obtained, from which can be isolated, by repeated recrystallisation, derivatives whose melting points were depressed in admixture with those of the 4-methylhex-4-en-1-ols obtained from other sources, and are therefore considered to be derived from 4-methylhex-*cis*-4-en-1-ol, which must be predominant in the product. We attribute this result to the use in the trimethylene oxide reaction of a higher reaction temperature than in the carbonation; this accentuates the tendency shown in the latter reaction for the formation of compounds derived from the *trans*-bromide. A similar thermal effect is shown in the carbonation of 2-lithiooctane [25] (from (−)-2-iodo-octane) which proceeds with partial retention of configuration at −70° but with complete racemisation if the intermediate organometallic compound is allowed to warm to 0°. If it is accepted [26] that retention of configuration normally occurs in both the formation and the reaction of the alkenyl-lithiums, and that the reaction proceeds *via* a carbanion intermediate, then the retention of configuration by the latter

[23] Searles, *J. Amer. Chem. Soc.*, 1951, **73**, 124.
[24] Dreiding and Pratt, *ibid.*, 1954, **76**, 1902.
[25] Letsinger, *ibid.*, 1950, **72**, 4842.
[26] Braude, " Progress in Organic Chemistry, Vol. III," Butterworths, London, 1955, p. 193.

must be temperature-dependent. Thus 2-lithiobut-*cis*- and -*trans*-2-ene (XXIII and XXIV) can give rise to the carbanions (XXI and XXII) which would be in equilibrium, with the more stable *trans*-form (XXII) predominating at the higher temperature, which would give rise to 4-methylhex-*cis*-4-en-1-ol (XX).

On the basis of the above results, although no rigid proof is available of the configuration of the 4-methylhex-4-en-1-ol obtained by the ring fission of 3-chlorotetrahydro-2 : 3-dimethylpyran (IX), the results are consistent with its being the pure *trans*-isomer.

The infrared spectra of *cis*- and *trans*-isomers containing a trisubstituted double bond have not been extensively studied [27] and the infrared spectra of our compounds have not been sufficiently distinct for this method to be useful for the allocation of configurations or for differentiation between the isomers.



Various mechanisms have been suggested [28,29] for the ring fission of 3-halogenotetrahydropyrans. Any mechanism proposed must account for the fact that both *cis*- and *trans*-2-alkyl-3-chlorotetrahydropyran and, as we have shown, 3-chlorotetrahydro-2 : 3-dimethylpyran yield *trans*-alk-4-en-1-ols. Crombie and Harper [29] have put forward such a mechanism, but a better insight into a possible mechanism is obtained by a study of the conformations of the reactants.

If it is accepted that the tetrahydropyran ring exists in a chair form,[30] then in the substituted 3-chlorotetrahydropyran in which the 3-chlorine and the 2-hydrogen atom are *cis* to each other the two possible conformations are (XXV) and (XXVI). Models show that in (XXV) there is interaction between the 2-methyl group and the axial 6-hydrogen atom and that (XXVI) is therefore the preferred conformation. In the latter, the equatorial 3-chlorine atom, $C_{(3)}$, $C_{(2)}$, and the oxygen atom are coplanar (see XXVII). This arrangement meets the steric requirements [31] for a concerted *trans*-elimination of chlorine and alkoxyl. This would be initiated by nucleophilic attack of the surface electrons of the sodium on the chlorine atom followed by electron-recession to $C_{(2)}$, then fission of the $C_{(2)}$–oxygen bond with release of two sodium ions. The resultant alk-4-en-1-ol (XXVIII) would have a *trans*-configuration. This mechanism is an elaboration of that suggested by Crombie and Harper.[29] For ring fission of the stereoisomeric substituted 3-chlorotetrahydropyran (2-hydrogen and 3-chlorine *trans*) to yield the *trans*-alk-4-en-1-ol (XXVIII), *cis*-elimination must occur. A study of models of the

[27] Bellamy, " Infra-red Spectra of Complex Molecules," Methuen, London, 1954.
[28] Paul, *Bull. Soc. chim. France*, 1933, **53**, 421; 1935, **2**, 745; Robinson and Smith, *J.*, 1936, 195; Amstutz, *J. Org. Chem.*, 1944, **9**, 310.
[29] Crombie and Harper, *J.*, 1950, 1707, 1714.
[30] Reeves, *J. Amer. Chem. Soc.*, 1949, **71**, 215, 2116.
[31] Ingold, " Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, 1953, p. 465.

possible conformations (XXIX) and (XXX) shows that in the former there is steric interference between the 2-methyl group, the 3-chlorine atom, and the axial 6-hydrogen atom, and the latter is therefore the preferred conformation. In (XXX) the 3-chlorine, $C_{(3)}$, $C_{(2)}$, and the oxygen atom are not coplanar (see XXXI) and a concerted *trans*-elimination is not sterically probable. The reaction might therefore proceed non-concertedly as proposed by Crombie and Harper [29] whereby $C_{(2)}$ becomes a carbonium ion and steric factors promote the formation of the *trans*-alk-4-en-1-ol (XXVIII) rather than a *cis-trans*-mixture of alkenols. An alternative mechanism is that owing to the close proximity of the axial 3-chlorine atom and the oxygen atom in conformation (XXX) (cf. XXXI), these atoms may make contact simultaneously with the surface of the sodium and a direct *cis*-elimination reaction, *via* a cyclic transition state (cf. ref. 32), may take place to yield the *trans*-alkenol (XXVIII). The above considerations account satisfactorily for the stereospecificity of the ring scission of substituted 3-halogenotetrahydropyrans by sodium.

Models show that when the 2-alkyl group in the above compounds is larger than methyl the same considerations apply and the ring scission by sodium of 2-alkyl-3-chlorotetrahydro-3-methylpyrans therefore constitutes a route to *trans*-alkenols of the type R·CH:CMe·CH_2·CH_2·CH_2·OH.

Experimental

(S) denotes distillation through a 30-plate spinning band column (Haage, Mulheim).

Petroleum denotes light petroleum (b. p. 60—80°).

Ethyl Propenyl Ether.—A mixture of heavy kaolin, Gooch asbestos, and water glass (10 : 2 : 4 by wt.), mixed with just sufficient water to bind it together, was spread on a sheet of asbestos paper and dried at 150° for 1 hr. The resulting semi-solid was broken into pieces (8/16 mesh) and loosely packed, together with a thermometer, into a 30 × 2 cm. Pyrex tube, arranged vertically in an electrically heated furnace. This packed tube was then heated at 300° for 2 hr. in a stream of dry nitrogen to complete drying of the catalyst. 1 : 1-Diethoxypropane (400 g.) was passed through the tube (340—350° int. temp.) at the rate of 2 small drops per sec. The product, collected over anhydrous potassium carbonate, was washed with ice-cold saturated sodium carbonate solution (2 × 200 ml.), dried (K_2CO_3), and distilled through a 30 × 2 cm. column packed with Dixon gauze; it yielded ethyl propenyl ether (144 g., 67·7% on acetal consumed), b. p. 66—72°, n_D^{20} 1·3965 (Deschamps *et al.*[9] record b. p. 68—70°, n_D^{20} 1·3965), together with 1 : 1-diethoxypropane (72 g.), b. p. 122—124°.

2-Ethoxy-2 : 3-dihydro-3-methyl-4H-pyran.—A mixture of redistilled acraldehyde (28 g., 0·5 mole), ethyl propenyl ether (60 g., 0·7 mole), and quinol (1·0 g.) was heated in an autoclave to 180°/11 atm. and kept at that temperature for 2 hr. The product was distilled under reduced pressure and the distillate fractionated through a 30 × 1 cm. column (as above) to give, after a forerun (6·0 g.), *2-ethoxy-2 : 3-dihydro-3-methyl-4H-pyran* (41 g., 57·5%), b. p. 149—152°, n_D^{20} 1·4356 (Found: C, 67·6; H, 9·95. $C_8H_{14}O_2$ requires C, 67·6; H, 9·8%).

2-Methylglutaraldehyde.—2-Ethoxy-2 : 3-dihydro-3-methyl-4*H*-pyran (12 g.) and 0·6N-hydrochloric acid (42·5 ml.) were stirred at 60° for 3 hr., then at room temperature for 3 hr., neutralised with sodium hydrogen carbonate solution, saturated with sodium chloride, and extracted with ether. Distillation of the dried ($MgSO_4$) extract gave 2-methylglutaraldehyde (3·4 g., 36%), b. p. 86—88°/17 mm., n_D^{20} 1·4345 [bis-*p*-nitrophenylhydrazone, orange plates (from ethanol), m. p. 162—164°; *bis-2 : 4-dinitrophenylhydrazone*, insoluble orange crystals (washed with ethanol, benzene, and chloroform), m. p. 194° (Found: C, 45·0; H, 4·1; N, 23·3. $C_{18}H_{18}O_8N_8$ requires C, 45·4; H, 3·8; N, 23·6%)]. Longley and Emerson [3] record b. p. 86—88°/17 mm., n_D^{25} 1·4330 (*p*-nitrophenylhydrazone, m. p. 167—169°).

Oxidation of 2-methylglutaraldehyde (cf. ref. 3) gave 2-methylglutaric acid, m. p. 75—77° undepressed on admixture with a authentic specimen.[33]

2-Ethoxytetrahydro-3-methylpyran.—2-Ethoxy-2 : 3-dihydro-3-methyl-4*H*-pyran (60 g.) in ethanol (60 ml.) was hydrogenated at 31°/20 atm. in the presence of 5% of Raney nickel. Removal of the catalyst and fractionation through a 30 × 2 cm. column (as above) gave

[32] Barton, *J.*, 1949, 2174.
[33] Ansell and Hey, *J.*, 1950, 1683.

2-ethoxytetrahydro-3-methylpyran (54·5 g., 90%), b. p. 152—153°/760 mm., 46°/12 mm., n_D^{20} 1·4244 (Found: C, 66·6; H, 11·3. $C_8H_{16}O_2$ requires C, 66·7; H, 11·1%). With Brady's reagent it gave the 2 : 4-*dinitrophenylhydrazone* of 5-hydroxy-2-methylpentanal as orange plates (from aqueous alcohol), m. p. 121—122° (Found: C, 48·45; H, 5·25. $C_{12}H_{16}O_5N_4$ requires C, 48·65; H, 5·4%).

5 : 6-*Dihydro-3-methyl-*4H-*pyran.*—2-Ethoxytetrahydro-3-methylpyran (95 g.) was pyrolysed at the rate of 1 drop/2 sec. as in the preparation of ethyl propenyl ether; on fractionation through a 30 × 2 cm. column (as above), and distillation from sodium, it gave 5 : 6-*dihydro-3-methyl-*4H-*pyran* (38 g., 59%), b. p. 111—113°, n_D^{20} 1·4456 (Found: C, 73·2; H, 10·3. $C_6H_{10}O$ requires C, 73·5; H, 10·2%). A fractionated (S) sample had b. p. 113·5°, n_D^{20} 1·4458. With Brady's reagent it gave the same derivative (m. p. 122—123°) as its precursor.

3-*Bromotetrahydro-*2 : 3-*dimethylpyran.*—Dry bromine (*ca.* 11·5 ml.) was added to a stirred solution of 5 : 6-dihydro-3-methyl-4*H*-pyran (20 g.) in dry ether (40 ml.) at −60° until a permanent yellow colour was obtained. This was removed by addition of a few drops of the dihydropyran. The ethereal solution of the crude dibromide was added to a stirred solution of methylmagnesium bromide (from magnesium, 7·3 g.) in ether (765 ml.) at such a rate that gentle refluxing was maintained. After being stirred for another 15 min. the mixture was poured on an excess of ice and ammonium chloride (12 g.). The ethereal layer was separated and the aqueous layer extracted with ether (2 × 50 ml.). Distillation of the dried ($MgSO_4$) combined extracts gave 3-bromotetrahydro-3-methylpyran (23·5 g., 64%), b. p. 78—82°/20 mm., n_D^{20} 1·4843. This material partially decomposed on attempted fractional (S) distillation (Found: C, 43·7; H, 7·2; Br, 40·3. Calc. for $C_7H_{13}OBr$: C, 43·5; H, 6·7; Br, 41·5%).

3-*Chlorotetrahydro-*2 : 3-*dimethylpyran.*—Dry chlorine was passed into a stirred solution of 5 : 6-dihydro-3-methyl-4*H*-pyran (20 g.) in dry ether (40 ml.) at −20° until a permanent green colour was obtained which was removed by the addition of a little of the dihydropyran. The subsequent procedure was as for the 3-bromo-analogue. The final distillation gave 3-*chlorotetrahydro-*2 : 3-*dimethylpyran* (28·7 g., 84%), b. p. 55—58°/12 mm., n_D^{20} 1·4571. Fractional (S) distillation gave material of b. p. 54—56°/17 mm., n_D^{20} 1·4580—1·4569 (Found: C, 56·8; H, 8·7. $C_7H_{13}OCl$ requires C, 56·6; H, 8·75%).

Ring Scission of 3-*Halogenotetrahydro-*2 : 3-*dimethylpyran.*—The 3-halogenotetrahydro-2 : 3-dimethylpyran (0·12 mole) was added to a stirred suspension of sodium sand (11 g.) in ether (30 ml.) at such a rate that steady refluxing was maintained. After a further 1 hour's stirring, water was cautiously added, the ethereal layer separated, and the aqueous layer extracted with ether. Distillation of the dried ($MgSO_4$) combined extracts gave 4-*methylhex-*trans-4-*en-*1-*ol* (5·2 g., 39% from 3-bromo-, 10 g., 74% from 3-chloro-compound), b. p. 75—78°/10 mm., n_D^{20} 1·4512. Fractional (S) distillation gave only material of b. p. 82°/16 mm., n_D^{20} 1·4512 (Found: C, 73·4; H, 12·7. $C_7H_{14}O$ requires C, 73·7; H, 12·3%). The derived α-*naphthylurethane* (plates from petroleum) had m. p. 76·5—77° (Found: C, 75·9; H, 7·7; N, 5·0. $C_{18}H_{21}O_2N$ requires C, 76·3; H, 7·5; N, 4·9%), and the 4-*diphenylylurethane* (laths from petroleum) had m. p. 97—98° (Found: C, 77·6; H, 7·3; N, 4·5. $C_{20}H_{23}O_2N$ requires C, 77·7; H, 7·4; N, 4·5%). Ozonolysis of the alcohol gave acetaldehyde, identified as the dimedone derivative, m. p. and mixed m. p. 140—141°. Hydrogenation (of 0·5 g.) in the presence of Adams catalyst gave 4-methylhexan-1-ol, n_D^{20} 1·4249 (α-naphthylurethane, m. p. 48·5—49°). Huston and Agett [10] record n_D^{23} 1·4233 (α-naphthylurethane, m. p. 50°).

The forerun, obtained only in the distillation of the alcohol from 3-bromotetrahydro-2 : 3-dimethylpyran, was redistilled from sodium to yield a dihydro-2 : 3-dimethylpyran (1·6 g.), b. p. 132—135°, n_D^{20} 1·4416 (Found: C, 75·3; H, 10·9. Calc. for $C_7H_{12}O$: C, 75·0; H, 10·8%). Sachs [34] records b. p. 131° for 5 : 6-dihydro-2 : 3-dimethyl-4*H*-pyran.

3-*Methylpent-*trans-3-*en-*1-*ol.*—Methyl 3-methylpent-*trans*-3-enoate [11] (100 g.) was added during 20 min. to a stirred suspension of lithium aluminium hydride (45 g.) in ether (1200 ml.) at 5°. After being boiled and stirred for 2½ hr. the mixture was cooled, and water added. The ethereal layer was decanted, and the residue washed by decantation with ether (3 × 200 ml.). The combined ethereal solutions were washed with saturated sodium chloride solution (100 ml.), dried (K_2CO_3), and distilled to yield 3-*methylpent-*trans-3-*en-*1-*ol* (70 g., 90%), b. p. 63—65°/15 mm., n_D^{20} 1·4466. A fractionated (S) sample had b. p. 155°, n_D^{20} 1·4467 (Found: C, 71·5; H, 12·15. $C_6H_{12}O$ requires C, 71·9; H, 12·1%). The derived α-*naphthylurethane* (laths from petroleum) had m. p. 78—78·5° (Found: C, 75·1; H, 7·0. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 7·1%).

[34] Sachs, *Ber.*, 1899, **32**, 62.

Ozonolysis of the alcohol gave acetaldehyde, identified as the dimedone derivative, m. p. and mixed m. p. 140—141°. Hydrogenation in the presence of Adams catalyst gave 3-methylpentan-1-ol (α-naphthylurethane, m. p. 56°). Huston and Agett [10] record α-naphthylurethane, m. p. 58°.

3-*Methylpent*-cis-3-*en*-1-*ol*.—Dry chlorine (14 g.) was added to a stirred solution of 3-methylpent-*trans*-3-en-1-ol (20 g.) and antimony pentachloride (1·5 ml.) in chloroform (40 ml.) at −60°. The solution was stirred for 15 min., allowed to warm to room temperature, poured into water, and extracted with ether (2 × 50 ml.). The combined extracts were dried ($MgSO_4$) and distilled, to give 3 : 4-dichloro-3-methylpentan-1-ol (15 g., 44%), b. p. 90—102°/0·1 mm., n_D^{18} 1·4840. The above dichloride (15 g.) was added to a stirred solution of potassium hydroxide (9·5 g.) in propanol (60 ml.), and the mixture stirred at 90° for 15 hr. Water (100 ml.) was added, and the mixture extracted with ether (2 × 150 ml.), and dried ($MgSO_4$). The ethereal extracts were distilled to give 4-chloro-3-methylpent-*cis*-3-en-1-ol (3 g., 27%), b. p. 84—96°/12 mm., n_D^{19} 1·4660. The above chloroalkenol (3 g.) was added, during 15 min., to a stirred solution of sodium (3·5 g.) in redistilled liquid ammonia (50 g.). Excess of sodium was destroyed by solid ammonium chloride, and the solution obtained by addition of water was extracted with ether (2 × 20 ml.). The dried ($MgSO_4$) extracts were distilled, to give 3-*methylpent*-cis-3-*en*-1-*ol* (1·2 g., 54%), b. p. 64—65°/18 mm., n_D^{20} 1·4452 (Found: C, 71·4; H, 12·05. $C_6H_{12}O$ requires C, 71·9; H, 12·1%). The derived α-*naphthylurethane* (plates from petroleum) had m. p. 105° (Found: N, 5·4. $C_{17}H_{19}O_2N$ requires N, 5·2%). Ozonolysis of the alcohol gave acetaldehyde, identified as the dimedone derivative, m. p. and mixed m. p. 140—141°. Hydrogenation in the presence of Adams catalyst gave 3-methylpentan-1-ol (α-naphthylurethane, m. p. 56—56·5°).

1-*Iodo*-3-*methylpent*-trans-3-*ene*.—A mixture of toluene-*p*-sulphonyl chloride (21 g.) and pyridine (10 g.) was warmed to 40°, then cooled rapidly to 0° with stirring and allowed to warm to room temperature. 3-Methylpent-*trans*-3-en-1-ol (10 g.) was added to the stirred suspension at 5—25°. After being stirred for a further 1 hr. the mixture was poured into water and extracted with ether (2 × 100 ml.), and the extract washed with 25% sulphuric acid (100 ml.), then saturated sodium hydrogen carbonate solution (100 ml.), and dried ($MgSO_4$). The residue left on removal of the solvent was heated at 100°/10^{-2} mm. for 30 min., to yield the derived toluene-*p*-sulphonate (22 g.). The latter was added to a stirred solution of sodium iodide (15 g.) in dry acetone (150 ml.), and the mixture heated under reflux for 3½ hr., then left overnight at room temperature. The ice-cold suspension was filtered and the residue washed with ether. After removal of solvent, the residue was washed with 10% aqueous sodium thiosulphate solution (2 × 30 ml.), dried ($MgSO_4$), and distilled, to yield 1-*iodo*-3-*methylpent*-trans-3-*ene* (11·5 g., 65%), 61—62°/16 mm., n_D^{20} 1·5236 (Found: C, 34·7; H, 5·7. $C_6H_{11}I$ requires C, 34·5; H, 5·3%).

4-*Methylhex*-trans-4-*en*-1-*ol*.—Formaldehyde [from dry paraformaldehyde (15 g.) heated at 180°] was carried in a stream of dry nitrogen into a stirred solution of the Grignard reagent from the above iodide (34·5 g.) and magnesium (4 g.) in ether (100 ml.). After 30 min. the mixture solidified. Ice and ammonium chloride solution were added, the ethereal layer was separated, and the aqueous layer was extracted with ether (3 × 50 ml.). Fractional distillation (S) of the dried ($MgSO_4$) combined extracts gave 4-methylhex-*trans*-4-en-1-ol (2·5 g., 15%), b. p. 80°/17 mm., n_D^{20} 1·4520 (Found: C, 73·5; H, 12·2. Calc. for $C_7H_{14}O$: C, 73·7; H, 12·3%). The derived α-*naphthylurethane* (plates from petroleum) had m. p. 75·5—76·5° alone or on admixture with the derivative of the alcohol obtained in the ring fission experiment (Found: N, 5·0. Calc. for $C_{18}H_{21}O_2N$: N, 4·9%). Ozonolysis of the alcohol gave acetaldehyde, identified as the dimedone derivative, m. p. and mixed m. p. 140—141°. Hydrogenation in the presence of Adams catalyst gave 4-methylhexan-1-ol, n_D^{23} 1·4237 (α-naphthylurethane, m. p. 48—49°).

4-*Methylhex*-4-*en*-1-*ol from Tiglic Acid*.—3-Methylbut-*trans*-3-en-1-ol,[35] prepared by reduction of tiglic acid,[17] was treated with phosphorus tribromide and pyridine,[36] and the resulting pentenyl bromide (90 g.), was added slowly to a stirred solution of sodiomalonic ester from ethyl malonate (95 g.) and sodium (13·7 g.) in alcohol (150 ml.), and the solution then stirred and boiled for 24 hr. Water was added to the cold solution, to dissolve the precipitated sodium bromide, and the mixture was extracted with ether (3 × 100 ml.). Distillation of the dried ($MgSO_4$) extracts gave a C_{12}-alkenyl-malonic ester (84 g., 60·5%), b. p. 129—132°/14 mm.,

[35] Hatch and Noyes, *J. Amer. Chem. Soc.*, 1957, **79**, 345.
[36] Cf. Lauchenauer and Schinz, *Helv. Chim. Acta*, 1951, **34**, 1514.

n_D^{20} 1·4404 (Found: C, 63·7; H, 8·75. Calc. for $C_{12}H_{20}O_4$: C, 63·2; H, 8·8%). This ester (75 g.) was added, with stirring, to a cold solution of potassium hydroxide (67 g.) in water (100 ml.), followed by sufficient alcohol to produce homogeneity. After 15 hr. at room temperature, the solution was concentrated to half bulk under reduced pressure, cooled to 0°, made just acid to Congo-red with concentrated hydrochloric acid, and extracted with ether (4 × 50 ml.). The crude dicarboxylic acid obtained on evaporation of the dried ($MgSO_4$) extracts was decarboxylated at 150° ± 5° for 2 hr. The product was dissolved in saturated sodium hydrogen carbonate solution and, after re-extraction with ether (3 × 100 ml.), the solution was acidified at 0° by stirring it with an equal volume of hexane and cautiously adding concentrated hydrochloric acid. The hexane layer was separated, and the aqueous layer extracted with hexane. Distillation of the dried ($MgSO_4$) extracts gave a C_7-alkenoic acid (21·5 g., 51%), b. p. 112—114°/12 mm., n_D^{20} 1·4472 (Found: C, 65·7; H, 9·7. Calc. for $C_7H_{12}O_2$: C, 65·6; H, 9·4%). The acid (20 g.) in ether (40 ml.) was added to a stirred suspension of lithium aluminium hydride (8·5 g.) in ether (200 ml.) at such a rate that vigorous refluxing occurred. After being boiled and stirred for a further ½ hr. the mixture was cooled, water added, and the ethereal solution decanted. The residue was washed by decantation with ether (2 × 25 ml.), and the dried ($MgSO_4$) combined extracts when distilled gave 14 g. of material, b. p. 84—86°/18 mm. The latter on fractional distillation (S) gave:

Fraction	B. p./14·5 mm.	Wt. (g.)	n_D^{20}	Infrared absorption at 887 and 1650 cm.$^{-1}$
1	72—75°	1·2	1·4419	Strong
2	75—79·5	3·4	1·4450	Medium
3	79·5—80·5	2·3	1·4490	Absent
4	80·5	4·2	1·4512 *	Absent

* Constant for 6 fractions.

Fraction 4 was accepted as 4-methylhex-*trans*-4-en-1-ol (Found: C, 73·55; H, 12·1. Calc. for $C_7H_{14}O$: C, 73·7; H, 12·3%). The derived α-naphthylurethane (plates from petroleum) had m. p. 76·5—77° (Found: N, 4·6. Calc. for $C_{18}H_{21}O_2N$: N, 4·9%), and the 4-diphenylylurethane (laths from petroleum) had m. p. 97—98° (Found: C, 77·5; H, 7·5; N, 4·6. Calc. for $C_{20}H_{23}O_2N$: C, 77·7; H, 7·4; N, 4·5%). The m. p.s of these derivatives were not depressed on admixture with the corresponding derivatives of the alcohol obtained by ring scission. Ozonolysis of the alcohol gave acetaldehyde (dimedone derivative, m. p. and mixed m. p. 140—141°). Hydrogenation in the presence of Adams catalyst gave 4-methylhexan-1-ol, n_D^{23} 1·4237 (α-naphthylurethane, m. p. 48—49°) (see above for previously recorded constants).

4-Methylhex-4-en-1-ol from Angelic Acid.—2-Methylbut-*cis*-2-en-1-ol (35 g.) obtained (by reduction [35] of angelic acid [17]) and pyridine (7 g.) were added to redistilled phosphorus tribromide (44 g.) at 0° during 30 min. and the mixture stirred at 0° for 1 hr., left overnight, and distilled at 15 mm. The crude distillate was dissolved in ether (50 ml.), washed with 10% aqueous sodium hydrogen carbonate (100 ml.) and water (50 ml.), dried ($MgSO_4$), and distilled, to give a pentenyl bromide (42 g., 70%), b. p. 124—130°, n_D^{20} 1·4794. The bromide was added to a stirred solution of sodiomalonic ester [from ethyl malonate (48 g.) and sodium (6·9 g.) in alcohol (90 ml.)], and the solution treated as above. Distillation of the product gave a C_{12}-alkenyl-malonic ester (41 g., 59%), b. p. 132—140°/23 mm., n_D^{20} 1·4400. This ester (41 g.) was stirred into a cold solution of potassium hydroxide (37 g.) in water (50 ml.) and ethanol (10 ml.), and after 7 days at room temperature was treated as above, to yield a crude oily dicarboxylic acid. The acid was decarboxylated at 150° ± 5° for 2 hr. and the product purified as before, to yield on distillation a C_7-alkenoic acid (9 g., 40%), b. p. 128—132°/45 mm., n_D^{20} 1·4468. This acid (9 g.) was dissolved in ether (20 ml.), added to a stirred suspension of lithium aluminium hydride (3·5 g.), and the mixture was boiled and stirred for ½ hr. The residue was purified as before and distilled, to give 4 g. of material, b. p. 90—94°/34 mm. The latter on fractional distillation (S) gave:

Fraction	B. p./15·5 mm.	Wt. (g.)	n_D^{20}	Infrared absorption at 887 and 1650 cm.$^{-1}$
1	71—75°	0·4	1·4420	Strong
2	75—79	0·5	1·4448	Medium
3	79—79·5	1·1	1·4480	Weak
4	79·5	1·7	1·4504	Absent

Fraction 4 was accepted as predominantly 4-methylhex-*trans*-4-en-1-ol (Found: C, 75·3; H, 12·5. Calc. for $C_7H_{14}O$: C, 73·7; H, 12·3%). The derived α-naphthylurethane (plates from petroleum) had m. p. 73·5—74·5° (Found: C, 76·3; H, 7·55; N, 5·0. Calc. for $C_{18}H_{21}O_2N$: C, 76·3; H, 7·5; N, 4·9%), and the 4-diphenylylurethane (laths from petroleum) had m. p. 94—95°. Mixed m. p.s of these derivatives with those of the alcohol from the ring fission were 76—77° and 95—96° respectively. Ozonolysis of the alcohol gave acetaldehyde (dimedone derivative, m. p. and mixed m. p. 140—141°). Hydrogenation in the presence of Adams catalyst gave 4-methylhexan-1-ol, n_D^{23} 1·4240 (α-naphthylurethane, m. p. 48·5—49·5°).

4-Methylhex-4-en-1-ols from cis- *and* trans-*2-Bromobut-2-ene.*—Freshly distilled 2-bromobut-2-ene (80 g., 0·59 mole) was added during 1 hr. to a stirred suspension of lithium (9 g., 1·3 mole) in ether (1000 ml.) at −20° to −15° under nitrogen, and the mixture then stirred for a further 15 min. at −10°. A solution of trimethylene oxide [37] (37·8 g.) in ether (100 ml.) was added at this temperature and the mixture was then boiled and stirred under reflux for 1 hr. Benzene (750 ml.) was then added slowly while ether (*ca.* 1000 ml.) was distilled off, and the solution then boiled and stirred for a further 2½ hr., left overnight, then hydrolysed by the addition of a saturated solution of ammonium chloride (200 ml.). The organic layer was separated, and the aqueous layer extracted with ether (3 × 100 ml.). Distillation of the dried ($MgSO_4$) combined organic material gave, from 2-bromobut-*trans*-2-ene, 4-methylhex-4-en-1-ol (51 g., 73%), b. p. 73—78°/14 mm., n_D^{20} 1·4500, a portion of which on fractional distillation (S) gave material, b. p. 78°/15 mm., n_D^{20} 1·4498—1·4506 (Found: C, 73·2; H, 12·4. Calc. for $C_7H_{14}O$: C, 73·7; H, 12·3%), which yielded acetaldehyde (dimedone derivative, m. p. and mixed m. p. 140—141°) on ozonolysis. The derived α-naphthylurethane (from petroleum) had m. p. 54·5—55·5°, raised to 61—65° after six recrystallisations (Found: C, 76·5; H, 7·4; N, 4·8. Calc. for $C_{18}H_{21}O_2N$: C, 76·3; H, 7·5; N, 4·9%), and the 4-diphenylylurethane (laths from petroleum) had m. p. 86—91°, raised to 93—95° after six recrystallisations (Found: C, 77·5; H, 7·3; N, 4·8. Calc. for $C_{20}H_{23}O_2N$: C, 77·7; H, 7·4; N, 4·5%). The organic material from 2-bromobut-*cis*-2-ene gave 4-methylhex-4-en-1-ol (39 g., 57·5%), b. p. 80—81°/17 mm., n_D^{20} 1·4506, a portion of which on fractional distillation (S) gave material, b. p. 78—78·5°/15·5 mm., n_D^{20} 1·4499—1·4507 (Found: C, 73·55; H, 12·6. Calc. for $C_7H_{14}O$: C, 73·7; H, 12·3%). The derived α-naphthylurethane (from petroleum) had m. p. 47—49·5°, raised to 65—67° after six recrystallisations (Found: C, 76·5; H, 7·8%), and the 4-diphenylylurethane (laths from petroleum) had m. p. 94—95° raised to 99·5—101° after six recrystallisations (Found: C, 77·4; H, 7·6; N, 4·8%). These derivatives depressed the m. p. to about 60° and 90° respectively on admixture with those of 4-methylhex-*trans*-4-en-1-ol.

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Chemistry Department, Queen Mary College, University of London, Mile End Road, London, E.1. [*Received, October 10th*, 1957.]

[37] Noller, *Org. Synth.*, Coll. Vol. III, p. 835.

686. *Gas-phase Eliminations. Part I. The Unimolecular Gas-phase Pyrolysis of Some Esters and Analogous Compounds.**

By Allan Maccoll.

Points of similarity and dissimilarity between the effects of α-methylation upon the rates of unimolecular pyrolysis of alkyl halides and of alkyl esters in the gas phase are discussed. It is suggested that gas-phase eliminations may be classified according to the importance of the bonds which are (*a*) broken or (*b*) formed in the transition state. When the two types are of roughly equal importance the reaction may be regarded as essentially homolytic. When the breaking bond, as in the case of the alkyl halides, or the forming bond as in the case of the esters, controls the reaction, and if the transition state is essentially polar, the mechanism is best thought of as being analogous to that of certain heterolytic reactions in solution.

The resemblance, shown in the literature, between the pyrolysis of esters and reactions of the corresponding halides is not surprising, since the reactions are formally similar: $>CH{-}CX< \longrightarrow >C{=}C< + HX$, where X is acyloxy or halogen. The analogy recently postulated [1] between homogeneous unimolecular dehydrohalogenation in the gas phase and substitution and elimination in a polar solvent raises the question how far similar mechanistic concepts apply to ester pyrolysis.

For pyrolysis of alkyl bromides two broad conclusions have emerged: (*a*) that elimination from primary alkyl bromides occurs by a mixed chain and unimolecular mechanism,[2,3] the former being effectively inhibited by *cyclo*hexene,[3,4] whereas (*b*) that from secondary [5] and tertiary bromides [6] is predominantly by a unimolecular mechanism.

Makens and Eversole [7] have studied ethyl formate, and Anderson and Rowley [8] *n*- and *iso*-propyl formate. Blades [9] has used the toluene-inhibition flow-technique to investigate ethyl formate and *iso*propyl formate. The Arrhenius parameters are as tabulated:

	Ethyl formate		*iso*Propyl formate	
E (kcal./mole)	40·01	44·14	44·23	44·0
10^{-13} A (sec.$^{-1}$)	$2{\cdot}52 \times 10^{-4}$	0·0213	0·247	0·38

For *n*-propyl formate, E (39·7 kcal. mole^{-1}) and A ($2{\cdot}94 \times 10^{9}$ sec.$^{-1}$) are very close to those for ethyl formate. It appears then, that primary esters undergo elimination by a mixed chain and unimolecular mechanism, as is the case for bromides.

Arrhenius parameters for the unimolecular decompositions of esters $R{\cdot}CO_2R'$ are set out in Table 1. From these, relative rates at 400° have been calculated, *viz.*: for variation of R, EtOAc/H·CO_2Et 0·97, Pr^{i}OAc/H·CO_2Pr^i 1·25, Et·CO_2Bu^t/Bu^{t}OAc 0·79; for variation of R′, Pr^{i}OAc/EtOAc 26, Bu^{t}OAc/EtOAc 515; H·CO_2Pr^i/H·CO_2Et 20, H·CO_2Bu^t/H·CO_2Et 720. Two conclusions can then be drawn: (*a*) variation of the group R has only a small effect on the rate, *i.e.*, the rate at which an ester decomposes is nearly independent of the acid from which it is derived (cf. Warwick and Fugassi [12]); (*b*) variation of group R′ has a marked effect, the esters being divided into three classes

* The subject matter of this paper was presented at the XVIth Internat. Congr. Pure Appl. Chem., Paris, 1957.

[1] Maccoll and Thomas, *Nature*, 1955, **176**, 392.
[2] Agius and Maccoll, *J.*, 1955, 973; Semenov, Sergeev, and Kapralova, *Doklady Akad. Nauk S.S.S.R.*, 1955, **105**, 301.
[3] Maccoll and Thomas, *J.*, 1957, 5073.
[4] (*a*) Thomas, (*b*) Harden and Maccoll, (*c*) Green, Maccoll, and Thomas, unpublished work.
[5] Maccoll and Thomas, *J.*, 1955, 979, 2445.
[6] Harden and Maccoll, *J.*, 1955, 2454; 1957, 5028; Harden, *J.*, 1957, 5024.
[7] Makens and Eversole, *J. Amer. Chem. Soc.*, 1939, **61**, 3203.
[8] Addison and Rowley, *J. Phys. Chem.*, 1943, **47**, 454.
[9] Blades, *Canad. J. Chem.*, 1954, **32**, 366.

depending upon whether the α-alkyl-carbon atom is primary, secondary, or tertiary, the rates for these differing by somewhat more than an order of magnitude.

TABLE 1. *Arrhenius parameters for unimolecular decomposition of esters* $R{\cdot}CO_2R'$.

R	R′	log *A*	*E* (kcal./mole)	Ref.	R	R′	log *A*	*E* (kcal./mole)	Ref.
H	Et	11·33	44·1	9	Me	Pr^i	13·00	45·0	9
H	Pr^i	12·58	44·0	9	Me	Bu^t	12·80	39·2	11
		12·33	44·2	8	Et	Bu^t	13·34	40·5	12
H	Bu^t	11·10	34·6	10	Ph	Menthyl	11·00	38·1	13
Me	Et	12·49	47·8	9					

TABLE 2. *Relative rates of pyrolysis at* 400°.

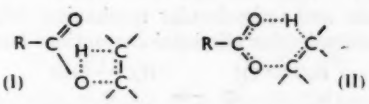
Class	Et	Pr^i	Bu^t	Ref.	Class	Et	Pr^i	Bu^t	Ref.
Chlorides ...	1	178	19,500	1	Acetates	1	26	515	9, 11
Bromides ...	1	170	32,000	1	Formates	1	20	720	8, 9, 10

The relative rates for the esters are compared in Table 2 with those for the chlorides and bromides. The trends are similar, suggesting an underlying common effect of α-methyl substitution. However the effect is much smaller for esters and, as will be seen below, this provides a clue to the mechanism. It is interesting that in each case the rate ratio for the *tert.*-butyl compound is approximately the square of that for the *iso*propyl compound, indicating that the effect is approximately linear with respect to the activation energy.

Szwarc and Murawski [14] have shown that acetic anhydride decomposes cleanly and by a unimolecular mechanism to acetic acid and keten. The rate constant is given by $\log k_1 = 12{\cdot}1 - 34{,}500/2{\cdot}303RT$. The activation energy is about 13 kcal. less than for ethyl acetate. The rate ratio with respect to ethyl acetate is 5600.

In a series of papers on the pyrolysis of esters in a flow system, Bailey and his colleagues [15] report that the olefin produced is the ethylene that carries the least number of alkyl substituents. Thus, *sec.*-butyl acetate would yield predominantly but-1-ene, while *tert.*-amyl acetate would yield 2-methylbut-1-ene. Bailey has pointed out that gas-phase elimination from esters follows the Hofmann rule.

The salient features that emerge from a survey of known unimolecular eliminations from esters are: (1) The rate sequence is $Me_3C > Me_2CH > Me{\cdot}CH_2$, but with a very much reduced spread than for halides. (2) The direction of elimination is governed by the Hofmann rule, in distinction to the behaviour of alkyl halides in the gas phase. (3) Acetic anhydride decomposes much faster than ethyl acetate. Before considering these facts in the light of electronic theory, previous ideas on the nature of the transition state in ester eliminations require mention. Two transition states have been suggested, namely, (I) and (II), involving respectively four and six centres. Warwick and Fugassi [21]



(I) (II)

dismiss (I) on the grounds that the pre-exponential term in the Arrhenius equation should be low, that is considerably less than the " normal " value of 10^{13} sec.$^{-1}$. Superficially this argument appears to be invalidated by the behaviour of the halides, for which the frequency factors are $\sim 10^{13}$ sec.$^{-1}$. However, in this case, the transition state is best regarded as a pseudo-four-centre system, to which the idea of rigidity and consequent large negative entropy of activation does not apply. On the other hand, formulation (II) is

[10] Gordon, Price, and Trotman-Dickenson, *J.*, 1957, 2813.
[11] Rudy and Fugassi, *J. Phys. Chem.*, 1948, **52**, 357.
[12] Warwick and Fugassi, *ibid.*, 1948, **52**, 1314.
[13] Barton, Head, and Williams, *J.*, 1953, 1715.
[14] Szwarc and Murawski, *Trans. Faraday Soc.*, 1951, **47**, 268.
[15] Bailey and King, *J. Org. Chem.*, 1956, **21**, 858, and references cited there.

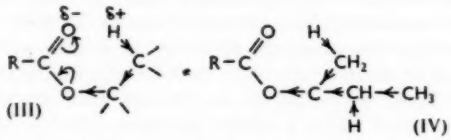
favoured by the largely unstrained six-membered ring, and subsequent discussion will be built on the basis of (II).

The key to the electronic interpretation of the reaction is Bailey's observation that the olefin production is governed by the Hofmann rule. In discussing elimination from sulphonium salts by the bimolecular mechanism (*E*2), Ingold [16] pointed out that the observed Hofmann orientation implies inductive control of the reaction. Three pieces of evidence suggest that this also applies to ester pyrolysis in the gas phase: (*a*) the Hofmann orientation; (*b*) a surprising analogy in the effect of α-methyl substitution in the two cases (cf. Table 3); (*c*) the marked effect of the carbonyl group in acetic anhydride (see above) (Me·CO·O·**CO**·Me *versus* Me·CO·O·**CH_2**·Me), replacement of CH_2 by CO

TABLE 3. *Relative rates in gas-phase and E2 eliminations.*

Compound	Ethyl	*iso*Propyl	*tert.*-Butyl
Formate (400°)	1	20	720
Acetate (400°)	1	26	515
Alkylsulphonium ion (45°)	1	23	586

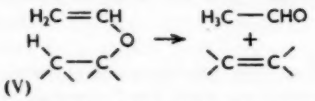
causing a strong inductive withdrawal of electrons from the β-hydrogen atom which, as will be seen below, will augment the effect of the carbonyl-oxygen atom. This evidence suggests that the reactions are best considered as a nucleophilic attack of the acyl-oxygen atom on the β-hydrogen atom. In other words, it is the *forming* O–H bond that primarily determines the rate, and not the breaking alkyl–oxygen bond. The transition state may then be represented as (III). α-Methyl substitution would tend to stabilise such a



(III) (IV)

transition state, accounting for the increase in rate in the α-methylated series. The effect of β-methylation in producing the greater proportion of the terminally unsaturated olefin is explained by the inductive protective action of the β-methyl group on the *sec.*-C–H bond [16] [(cf. (IV)]. It will be noted that the mechanism suggested for the esters is in marked contrast with that postulated for halides, where the dominating factor is the *breaking* C–X bond.

A further reaction for which a six-centred transition state has been postulated, and which shows a quantitative analogy with the pyrolysis of esters, is pyrolysis of alkyl vinyl ethers. *n*-Butyl and *iso*butyl vinyl ether have been shown by Molera and Quiros [17] to decompose by a mixed chain and unimolecular mechanism (cf. primary bromides and esters). In two cases the unimolecular elimination reactions have been isolated, namely



(V)

for ethyl vinyl [18] (V) and *iso*propyl vinyl ether.[19] The reaction is clean, and follows the annexed scheme. The Arrhenius parameters are compared in Table 4 with those of the corresponding esters. The rate ratios of the *iso*propyl to the ethyl compound are respectively 20 and 17. This evidence suggests a similarity of mechanism. Since ethyl formate and ethyl vinyl ether differ only by the replacement of an oxygen atom by a

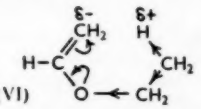
[16] Ingold, " Structure and Mechanism in Organic Chemistry," Bell, London, 1953.
[17] Molera and Quiros, XVIth Internat. Congr. Pure Appl. Chem., Paris, 1957.
[18] Blades and Murphy, *J. Amer. Chem. Soc.*, 1952, **74**, 1039; cf. Wang and Winkler, *Canad. J. Res.*, 1943, **218**, 97.
[19] Blades, *Canad. J. Chem.*, 1953, **31**, 418.

methylene group [H·C**O**·OEt, H·C(:**CH$_2$**)·OEt]. The conclusion is that the reaction is essentially a nucleophilic attack on the β-hydrogen atom by the $CH_2^{\delta-}$ group as shown in the representation (VI). The behaviour of alkyl vinyl ethers contrasts sharply with that of diethyl ether or divinyl ether,[20] for which no such mechanism is possible. Diethyl

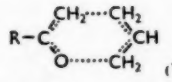
TABLE 4. *Arrhenius parameters for pyrolysis of formates and vinyl ethers.*

	Formate		Vinyl ether	
	log *A*	*E* (kcal./mole)	log *A*	*E* (kcal./mole)
Ethyl	11·33	44·1	11·43	43·6
*iso*Propyl	12·58	44·0	12·58	43·6

ether [21] decomposes in part by a chain mechanism, whereas pyrolysis of divinyl ether is by a complex mechanism, involving free radicals.[22]



(VI)



(VII)

The reactions of allyl vinyl [23] and allyl *iso*propenyl ether [24] have also been studied in the gas phase. These compounds rearrange at roughly the same rate, to give pent-4-enal and hex-5-en-2-one, respectively, the suggested transition state being (VII). This similarity in rate might be expected since the only difference is methyl-substitution at the centre of a three-atom mesomeric system. The Arrhenius parameters reported were 30·6 kcal./mole and 5×10^{11} sec.$^{-1}$, and 29·3 kcal./mole and $5{\cdot}4 \times 10^{11}$ sec.$^{-1}$, respectively. It is of interest that allyl *p*-tolyl ether rearranges in solution in diphenyl ether with Arrhenius parameters of roughly the same value (33·1 kcal./mole and $1{\cdot}6 \times 10^{11}$ sec.$^{-1}$).[25] No data exist to show the effect of α-methylation in the allyl group.* It can be suggested that in reactions of this type both the forming and the breaking bond are of importance in determining the kinetics of the reaction, as has indeed been done by Ingold.[16]

This raises the question of the possibility of distinguishing between homolytic and heterolytic mechanisms in cyclic transition states. Hughes and Ingold,[26] referring to reactions proceeding in solution through a cyclic transition state, state that " it is unphysical to try to classify intramolecular rearrangements as exclusively electrophilic or nucleophilic or even heterolytic or homolytic . . . though cases may arise in which one character seems to predominate." The present discussion points out some cases in which the distinction can reasonably be made for gas-phase reactions. In general, if the cyclic transition state of a gas reaction can be represented by the structures (VIII) and (IX),

(VIII) (IX)

then the reaction may be best thought of as essentially homolytic. This is the case in which the forming and the breaking bond are of roughly equal importance. However,

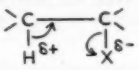
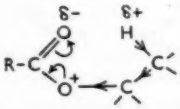
* *Added, July 21st,* 1958.—Goering and Jacobson (*J. Amer. Chem. Soc.*, 1958, **80**, 3277) have shown that α-methyl substitution increases the rate of rearrangement of allyl phenyl ethers in solution fourteenfold, as predicted by Rhoades and Crecilius (*ibid.*, 1955, **77**, 5057). I thank Professor H. L. Goering for sight of the manuscript before publication.

[20] Taylor, *J. Chem. Phys.*, 1936, **4**, 116.
[21] Smith and Hinshelwood, *Proc. Roy. Soc.*, 1942, *A*, **180**, 237; Steacie, " Atom and Free Radical Reactions," Reinhold, Publ. Inc., New York, 1954.
[22] Lossing, Ingold, and Henderson, unpublished work, referred to by Steacie.[21]
[23] Schuler and Murphy, *J. Amer. Chem. Soc.*, 1950, **72**, 3155.
[24] Stein and Murphy, *ibid.*, 1952, **74**, 1041.
[25] Kinkard and Tarbell, *ibid.*, 1939, **61**, 3085.
[26] Hughes and Ingold, *Quart. Rev.*, 1952, **6**, 34.

if the transition state is essentially characterized by a breaking bond (alkyl halides) or a forming bond (esters) and if this process is essentially polar in character, then it is reasonable to regard them as essentially heterolytic and to discuss the effect of structural variations in terms of the well-developed theories of organic reactions in solution.

This discussion may be summarized as in Table 5.

TABLE 5. *Transition states in gas-phase reactions.*

Type of reaction	Transition state	Solution analogue
Olefin elimination from halides		S_Ni
Claisen rearrangement		Similar to gas-phase, in non-polar solvents
Olefin elimination from esters		*E*2

Claisen-type rearrangement seems to involve a roughly equal status for the forming and the breaking bond. In the two extreme cases, halides and esters, α-methyl substitution alters the rate by one or two orders of magnitude respectively. A question, as yet unanswered, then arises whether the effect of such substitution in the intermediate case will lie between the two extreme ones or will be unrelated to either.

Conclusion.—This discussion bears out Maccoll and Thomas's general conclusion [1] that certain homolytic gas-phase reactions can be usefully discussed in terms of mechanism and structural effects that have been firmly established for heterolytic reactions in polar solvents, and that these reactions can be classified by the relative importance of bond-breaking and bond-forming in the transition state.

The author acknowledges the interest shown in the work by Professors E. D. Hughes, F.R.S., and Sir Christopher Ingold, F.R.S., and many stimulating discussions with Mr. V. R. Stimson.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, GOWER STREET, LONDON, W.C.2. [*Received, February 21st*, 1958.]

687. *The Thermodynamic Functions of Methyl Nitrite and the Potential Barrier to Free Rotation.*

By PETER GRAY and M. W. T. PRATT.

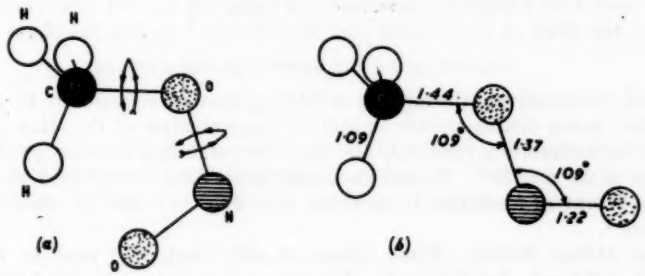
Methyl nitrite is an equilibrium mixture of the *cis*- and the *trans*-isomer, interconvertible by rotation about the O–N bond. At any specified temperature and pressure, their relative abundance is determined by the differences in their thermodynamic functions while their rate of interconversion is determined by the height of the potential-energy barriers which hinder the internal rotations of the molecule.

Equilibrium and thermochemical data are used to derive thermodynamic functions for the (gaseous) equilibrium mixture at 25° c and 1 atm. They are: $\Delta H_f^\circ = -14{,}930 \pm 260$ cal. mole^{-1}; $\Delta G_f^\circ = -450$ cal. mole^{-1} and $\Delta S_f^\circ = -48{\cdot}6$ cal. deg.$^{-1}$ mole^{-1}. The standard entropy relative to the crystal at absolute zero, S_{298}°, is thus $71{\cdot}5 \pm 0{\cdot}9$ cal. deg.$^{-1}$ mole^{-1}. Theoretical calculations of S_{298}°, based on the geometry of the isomers and their vibrational frequencies, lead to $S_{298}^\circ + S_b = 74{\cdot}1 \pm 0{\cdot}14$ cal. deg.$^{-1}$ mole^{-1}, *i.e.*, to $S_b = 2{\cdot}6 \pm 0{\cdot}9$ cal. deg.$^{-1}$ mole^{-1}, where S_b is the entropy "deficit" due to the hindrance imposed on rotation by the potential-energy barriers.

If the methyl group rotates freely about the C–O axis, the barrier hindering free rotation of the N=O group is about 8000 cal. mole^{-1}.

SPECTROSCOPY has recently demonstrated that rotational isomerism is a general property of alkyl nitrites. Tarte [1] studied the infrared and ultraviolet absorption spectra of fifteen nitrites. He found that the characteristic absorption bands of the O–N=O group were doublets in all cases and that the relative intensity of the constituents of the doublets changed with temperature. This is readily explained by the presence of two rotational isomers, having slightly different vibrational frequencies, whose relative abundance varies with temperature. Haszeldine and his co-workers interpret their spectroscopic work [2] on the nitrite esters by the same postulate of rotational isomerism.

Structures of cis- *and* trans-*methyl nitrite* (*a and b respectively*), *showing bond lengths* (Å) *and angles, and internal rotation.*



The infrared spectrum of methyl nitrite has been investigated further by Tarte,[3] and Wagner [4] has studied its Raman spectrum. It exists in two isomeric forms, in both of which the carbon, oxygen, and nitrogen atoms lie in the same plane. These are a *cis*-form (Figure *a*) and a *trans*-form (Figure *b*).

Since two rotational isomers of methyl nitrite can be distinguished, rotation about

[1] Tarte, *J. Chem. Phys.*, 1952, **20**, 1570; *Bull. Soc. chim. belges*, 1951, **60**, 227, 240.
[2] Haszeldine and Jander, *J.*, 1954, 691; Haszeldine and Mattinson, *J.*, 1955, 4172.
[3] Tarte, *Bull. Soc. chim. belges*, 1953, **62**, 401.
[4] Wagner, *Acta Physica Austriaca*, 1953, **8**, 175.

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the CH_3·O–NO single bond is not free but is opposed by a potential-energy barrier. The existence of this barrier must be reflected in the thermodynamic functions of methyl nitrite, for the entropy of a molecule having restricted rotation is less than that of the same molecule rotating freely. The entropy deficit depends directly upon the size of the barrier. The size of the barrier also determines the rate of *cis* $\rightleftharpoons$ *trans* interconversion but not the equilibrium proportions of the two species, which are decided by the *difference* between the potential-energy minima on either side of the barrier. In fact, as will be shown later, although the barrier to interconversion is large, the actual energy difference between the isomers is probably small, and may be only 100—200 cal. mole^{-1}.

In this paper, equilibrium and thermochemical data are used to derive "best" values of the standard thermodynamic functions of gaseous methyl nitrite (*cis–trans* equilibrium mixture) at 25° and 1 atm. and, from them, an "experimental" value of its standard entropy relative to absolute zero, $S_{298}°$. Next, a value of $S_{298}° + S_b$, where S_b is the entropy "deficit" due to restriction on free rotation, is calculated by the standard methods of statistical mechanics. In deriving this "calculated" value allowance is made for entropy of mixing and for deviations from ideal-gas behaviour. From the difference between the two values the sizes of the potential barriers to rotation are estimated.

Unless otherwise stated, all thermodynamic functions refer to the gaseous state at 25° and 1 atm.

Experimental values for the thermodynamic functions of methyl nitrite

Independent values of the heat ($\Delta H_f°$) and standard free energy of formation ($\Delta G_f°$) of methyl nitrite can be derived from existing experimental data, and by their combination yield the standard entropy of formation ($\Delta S_f°$): $T\Delta S_f° = -(\Delta G_f° - \Delta H_f°)$.

Standard Heat of Formation.—Baldrey, Lotzgesell, and Style [5] have recently measured and compared the heats of hydrolysis of pure methyl nitrite and of pure sodium nitrite: the unstable nitrous acid liberated during the reaction was immediately oxidised *in situ* by ceric sulphate to nitric acid. The value of ΔH_f of liquid methyl nitrite thus found is $-20{,}330 \pm 253$ cal. mole^{-1}.

They also measured ΔH_v, the latent heat of vaporization of methyl nitrite, finding $\Delta H_v = 5400 \pm 40$ cal. mole^{-1}. Thus, the standard enthalpy of formation of gaseous methyl nitrite $\Delta H_f° = 14{,}930 \pm 255$ cal. mole^{-1}.

Standard Gibbs Free Energy of Formation.—A value for $\Delta G_f°$ of methyl nitrite can be obtained from the work of Leermakers and Ramsperger [6] on the gas-phase equilibrium

$$CH_3·O·NO(g) + HCl(g) \rightleftharpoons CH_3·OH(g) + NOCl(g) \quad . \quad . \quad . \quad . \quad . \quad (1)$$

They measured quantitatively the amount of NOCl present at equilibrium by means of its light absorption, using stoicheiometry to find the concentration of the other components. They derived the equilibrium constant, and hence the standard free-energy change, $\Delta G°$, of the reaction at 25° and 50°. Modern thermodynamic data [7] being used, their result for the Gibbs free energy of formation is corrected from $\Delta G_f° = -100$ cal. mole^{-1} to $\Delta G_f° = -450$ cal. mole^{-1}.

Entropy of Methyl Nitrite.—These values of $\Delta H_f°$ and $\Delta G_f°$ lead to the result * $\Delta S_f° = -48{\cdot}6 \pm 0{\cdot}9$ cal. deg.$^{-1}$ mole^{-1}. The entropy of gaseous methyl nitrite at 25°

* By using the equation:

$$(\Delta S°/R) = (T_1 \ln K_1 - T_2 \ln K_2)/(T_1 - T_2),$$

a value for the average entropy change $\Delta S°$ over the temperature range 25—50° for reaction (1) could be obtained from Leermakers and Ramsperger's data alone. However, the precision of $\Delta S°$ so found from two readings only is too low for this work; the error is large and the "best" value obtainable leads to an absurdly large entropy deficit.

[5] Baldrey, Lotzgesell, and Style, personal communication.
[6] Leermakers and Ramsperger, *J. Amer. Chem. Soc.*, 1932, **54**, 1837.
[7] Nat. Bur. Stand. Circular 500, "Selected Values of Chemical Thermodynamic Properties," U.S. Dept. of Commerce, Washington, D.C., 1952.

and 1 atm. relative to that at absolute zero, $S_{298}°$, is calculated from this standard entropy of formation by means of the modern values [7] for the standard "absolute" entropies of the elements: it is $S_{298}° = 71{\cdot}5 \pm 0{\cdot}9$ cal. deg.$^{-1}$ mole^{-1}.

Calculation of the Entropy of Methyl Nitrite

Bond Lengths and Angles in Methyl Nitrite.—The only determination of the structure of methyl nitrite is that of Rogowski (Figure).[8] From the electron diffraction of the vapour he finds that the carbon, nitrogen, and both oxygen atoms lie in one plane, and that the molecule is "twice bent at the tetrahedral angle." * Rogowski's results are shown in Table 1 together with values of similar bond lengths and angles in other molecules.[10,11,12] Although 120° might be thought more likely on theoretical grounds for an RO–N=O interbond angle (because of the likelihood of trigonal hybridization of the electrons of the nitrogen atom), in fact it makes little difference whether it or the tetrahedral angle is accepted. The value supported by experiment is chosen here. The values for methyl nitrite agree fairly well with those [10] for other compounds, and are accepted for this calculation. The length of the tetrahedral C–H bonds is taken as 1·09 Å.

Table 1. *Bond lengths* (Å) *and angles in methyl nitrite compared with similar values in other molecules.*

	Bond length			*Interbond angle*	
Bond	In methyl nitrite	In other molecules	Bond	In methyl nitrite	In other molecules
C–O	1·44 ± 0·02	Of 22 compounds, mean 1·437 (range 1·40—1·46)	C–O–N	109° 28′	111° ± 3°, *O*-methylhydroxylamine
O–N	1·37 ± 0·02	1·36, pentaerythritol tetranitrate 1·37, *O*-methylhydroxylamine 1·41, nitric acid	O–N=O	109° 28′	114° ± 2°, *cis*-nitrous acid 118° ± 2°, *trans*-nitrous acid
N=O	1·22 ± 0·02	1·22, nitric acid 1·22, methyl nitrate 1·27, pentaerythritol tetranitrate			

Term-by-term Calculation of the Entropy.—The molar entropy of *cis*-methyl nitrite, S_{cis}, is the sum of translational, rotational, and vibrational contributions:

$$S_{cis} = (S_{transl} + S_{rot} + S_{vib})_{cis}$$

S_{rot} is the sum of contributions made by rotation of the whole molecule in three dimensions, S_p, and the internal rotations S_{int}:

$$(S_{rot} = S_p + S_{int})_{cis}$$

If S_f is the entropy contribution which would be made by the internal rotations of the molecule if they were completely unhindered, and S_b is the reduction in entropy caused by the existence of a potential-energy barrier to free rotation, which is assumed to be the same for both the *cis*- and the *trans*-form:

$$(S_{int})_{cis} = (S_f)_{cis} - S_b$$

Thus
$$S_{cis} = (S_{transl} + S_{vib} + S_p + S_f)_{cis} - S_b$$

Similarly
$$S_{trans} = (S_{transl} + S_{vib} + S_p + S_f)_{trans} - S_b$$

* It is erroneously reported by Allen and Sutton in their review [9] that Rogowski found the methyl nitrite molecule to be linear. This unfortunate error has found its way into the literature; see, *e.g.*, W. Klyne, "Progress in Stereochemistry," Butterworths, London, 1952.

[8] Rogowski, *Ber.*, 1942, *B*, **75**, 244.
[9] Allen and Sutton, *Acta Cryst.*, 1950, **3**, 46.
[10] Cox and Jeffrey, *Proc. Roy. Soc.*, 1951, *A*, **207**, 110.
[11] D'Or and Tarte, *Bull. Soc. roy. Sci. Liège*, 1951, Nos. 8–9–10, 478; Jones, Badger, and Moore, *J. Chem. Phys.*, 1951, **19**, 1599; Palm, *J. Chem. Phys.*, 1957, **26**, 855.
[12] Cohn, Ingold, and Poole, *J.*, 1952, 4272.

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After allowances for the entropy of mixing the two isomers in the correct proportions at 298° K and corrections for gas imperfection have been made, an expression is found for the entropy relative to that at absolute zero of the real equilibrium mixture, $S_0°$, in which all quantities except S_0 are known. The separate contributions are discussed individually below and the calculated entropy functions are in Table 2.

Contribution due to the translation and rotation of the molecule as a whole. Calculations of the contribution of translation to the entropy are conventional and the result is entered in Table 2. The error in S_{transl} is negligible. The expression for the rotational partition

TABLE 2. *Calculated entropy functions (cal. deg.$^{-1}$ mole^{-1}) of* cis- *and* trans-*methyl nitrite and of the equilibrium mixture.*

		cis	*trans*
Translation	S_{transl}	38·24 ± 0·00	38·24 ± 0·00
Rotation of the molecule as a whole	S_{rot}	23·29 ± 0·05	23·15 ± 0·05
Free internal rotations	S_f (N=O)	5·80 ± 0·04	5·80 ± 0·04
	S_f (CH_3)	3·58 ± 0·07	3·55 ± 0·07
Vibration	S_{vib}	1·95 ± 0·10	2·06 ± 0·10
Totals for the isomers		72·86 ± 0·14	72·80 ± 0·14
Maximum entropy of mixing		1·41	
Entropy of equilibrium mixture (ideal gas)		74·21 ± 0·14	
Correction for gas imperfection		−0·07	
Total for equilibrium mixture at 1 atm., 25° c	$S_{298}°$	74·1 ± 0·14	

function involves the product of the three principal moments of inertia, A, B, and C, of the molecule.

When allowance is made for the probable error in Rogowski's structural measurements,[8] it is calculated that for *cis*-methyl nitrite $ABC = (5·92 \pm 0·30) \times 10^{-115}$ g.^{3} cm.^{6} and for *trans*-methyl nitrite $ABC = (5·15 \pm 0·26) \times 10^{-115}$ g.^{3} cm.^{6}. From this $(S_{rot})_{cis} = 23·29 \pm 0·05$ and $(S_{rot})_{trans} = 23·15 \pm 0·05$ cal. deg.$^{-1}$ mole^{-1}.

Contribution due to internal rotation. There are two possible internal rotations in methyl nitrite as indicated in the Figure. These are rotation of the methyl group about the C–O bond and rotation of the N=O group about the O–N bond.

The contributions to the total entropy which these internal rotations make if they are perfectly free, S_f, may be calculated as follows. Let I_A be the moment of inertia of a molecular group about its axis of rotation and I_B be the moment about the axis of rotation of all the atoms except the group whose rotation is being considered. Then the reduced moment of inertia of the rotating group $I = I_A I_B/(I_A + I_B)$ and the formula quoted by Pitzer:[13]

$$S_f = R(-0·767 + \tfrac{1}{2} \ln T + \tfrac{1}{2} \ln I \times 10^{40} - \ln n)$$

enable the entropy contribution of the free internal rotation to be calculated. In this formula n, the number of potential energy minima of (approximately) equal depth passed through during one rotation, is taken as 3 for rotation of the CH_3 group, and 2 for rotation of the NO group. Errors due to assuming that the axes of rotation of the N=O and CH_3 groups coincide exactly with the O–N and C–O single bonds are negligible.

In Table 3 are shown the values of I and the entropy contributions, S_f, of the internal rotations of methyl nitrite. They are virtually identical for the two isomers.

Contribution due to vibration. A non-linear molecule of x atoms has $3x - 6$ vibrational modes and internal rotations. For methyl nitrite $x = 7$ and $3x - 6 = 15$. The two internal rotational modes have already been considered. Therefore, thirteen vibrational modes remain. The vibrational assignment is shown in Table 4. The sources used for this are principally the infrared spectral measurements by Tarte;[3] use is also made of

[13] Pitzer, *J. Chem. Phys.*, 1937, **5**, 469; see also Kemp and Pitzer, *J. Chem. Phys.*, 1936, **4**, 749; *J. Amer. Chem. Soc.*, 1937, **59**, 276.

the Raman shifts quoted by Wagner [4] and Hibben; [14] and, for some of the frequencies of the methyl group, the values given by Brand and Cawthon [15] for methyl nitrate, which are assumed to be identical with the corresponding vibrations in methyl nitrite. (As

TABLE 3. *Reduced moments of inertia and entropy contributions of freely rotating methyl and nitrosyl groups in methyl nitrite.*

Isomer	Rotating group	Reduced moment of inertia (g. cm.^{2})	Entropy contribution (cal. deg.$^{-1}$ mole^{-1})
cis	CH_3	$(5{\cdot}15 \pm 0{\cdot}20) \times 10^{-40}$	$3{\cdot}58 \pm 0{\cdot}07$
trans	CH_3	$(5{\cdot}00 \pm 0{\cdot}20) \times 10^{-40}$	$3{\cdot}55 \pm 0{\cdot}07$
cis and *trans*	N=O	$(21{\cdot}4 \pm 0{\cdot}8) \times 10^{-40}$	$5{\cdot}80 \pm 0{\cdot}04$

TABLE 4. *Vibrational assignment of* cis- *and* trans-*methyl nitrite.*

cis		*trans*			
Frequency ν (cm.$^{-1}$)	Contribution to S/R	Frequency ν (cm.$^{-1}$)	Contribution to S/R	Approximate description of vibration	Ref.
364	0·556	364	0·556	C–O–N bending	4, 14
617	0·212	565	0·263	O–N–O bending	3
844	0·088	814	0·099	N–O stretching	3
993	0·048	1045	0·039	C–O stretching	3
1630	0·003	1680	0·003	N=O stretching	3
1132	0·027	1132	0·027	CH_3 rocking	15
1176	0·023	1176	0·023	CH_3 rocking	15
1434	0·008	1434	0·008	CH_3 deformation	15
1468	0·007	1468	0·007	CH_3 deformation	15
1445	0·008	1370	0·010	CH_3 deformation	3
2944	0·000	2944	0·000	C–H stretching	14
3048	0·000	3048	0·000	C–H antisymm. stretch. (doubly degenerate)	14
Total contribution to S/R	0·980		1·035		

none of these methyl group vibrations makes a large entropy contribution, the error involved is negligible).

If ν_i represents the frequency of the ith vibrational mode of the molecule, then:

$$S_{vib}/R = \sum_{i=1}^{i=13} \{(h\nu_i/kT)[\exp(h\nu_i/kT) - 1] - \ln[1 - \exp(-h\nu_i/kT)]\}$$

Values of S/R for each of the thirteen vibrational modes and for the totals are shown in Table 4. The probable error in the totals is estimated to be less than $\pm 0{\cdot}1$ cal. deg.$^{-1}$ mole^{-1} and the values for the two isomers, $(S_{vib})_{cis} = 1{\cdot}95$ and $(S_{vib})_{trans} = 2{\cdot}06$ cal. deg.$^{-1}$ mole^{-1}, are not significantly different.

Contribution due to mixing of the two isomers. The entropy S_{mix} of an ideal mixture of two isomers, having molar entropies S_{cis} and S_{trans} and present in the mole fractions y and $(1 - y)$ respectively, is given by:

$$S_{mix} = y\,S_{cis} + (1 - y)\,S_{trans} - R\{y \ln y + (1 - y) \ln (1 - y)\}$$

The maximum value which this expression for S_{mix} can take occurs when $y = 1 - y$, *i.e.*, in an equimolar mixture, and is $S_{mix} = 74{\cdot}21 - S_b$. The exact value of the relative abundance of the isomers is discussed in the Appendix; but because S_{mix} is relatively insensitive to this ratio (S_{mix} differs only by 0·37 cal. deg.$^{-1}$ mole^{-1} from the maximum value for *cis* : *trans* ratios varying from 1 : 4 to 4 : 1) its exact value is unimportant in this calculation. In Table 2, the maximum value is entered. The point receives further discussion in the Appendix.

Effect of gas imperfection. The calculated entropy of methyl nitrite does not allow

[14] Hibben, "The Raman Effect and its Chemical Applications," Reinhold, New York, 1939, p. 285.
[15] Brand and Cawthon *J. Amer. Chem. Soc.*, 1955, **77**, 319.

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for the departure from ideality of methyl nitrite vapour, and a correction [16] is made for this by using the modified Berthelot equation:

$$(S_{ideal} - S_{real})/R = (27/32)(T_c/T)^3(P/P_c)$$

For methyl nitrite, the critical temperature (T_c) is estimated as 380° K, and the critical pressure (P_c) as 50 atm. The correction is therefore 0·07 cal. deg.$^{-1}$ mole^{-1}. This is subtracted from the calculated entropy, so that both it and the experimentally derived entropy refer to the real vapour.

From the sum of all the above terms, listed in Table 2, the entropy at 25° C and 1 atm. of an equilibrium mixture of methyl nitrite is, relative to that at absolute zero, $S_{298}^\circ + S_b = 74{\cdot}1 \pm 0{\cdot}14$ cal. deg.$^{-1}$ mole^{-1}.

The Magnitude of the Barriers to Free Rotation.—The calorimetric and equilibrium data give $S_{298}^\circ = 71{\cdot}5 \pm 0{\cdot}9$ cal. deg.$^{-1}$ mole^{-1}, and the calculated terms above lead to $S_{298}^\circ + S_b = 74{\cdot}1 \pm 0{\cdot}14$ cal. deg.$^{-1}$ mole^{-1}. Therefore the maximum value of the reduction in entropy below that of a freely rotating molecule caused by the potential barriers is $S_b = 2{\cdot}6 \pm 0{\cdot}9$ cal. deg.$^{-1}$ mole^{-1}.

The height of the potential-energy barrier hindering free rotation to which this entropy deficit corresponds can be derived from Pitzer's [13] tabulated results. The entropy reductions relative to free rotation (in parentheses, cal. deg.$^{-1}$ mole^{-1}) due to hindered rotation of the nitrosyl group about the O–N bond for various barrier-heights (cal. mole^{-1}) are: 1000 (0·3), 2000 (0·9), 3000 (1·4), 6000 (2·3), 9000 (2·7), 12,000 (3·1). Thus, to cause an entropy reduction of 2·6 cal. deg.$^{-1}$ mole^{-1}, rotation of the nitrosyl group must be opposed by a potential-energy barrier of 7800 cal. mole^{-1}.

Discussion

Interpretation of the size and origin of the potential-energy barrier to free rotation in methyl nitrite is assisted by two comparisons. The first is of the place of methyl nitrite in relation to other nitrite esters and to nitrous acid; the second is the relation of the nitrite family to other, chemically similar, homologous series such as the nitrate esters and the nitrosamines. Since this work was done, both these aspects have been illuminated by the application of high resolution nuclear (proton) magnetic resonance spectroscopy.

We examine first the size of the potential energy barrier and next its origin. The problem of the relative stability and abundance of the two isomers, and its relevance to the entropy of mixing, is considered in the Appendix.

The Size of the Energy Barrier to Free Rotation.—The size of the barrier, $V_b = 7800$ cal. mole^{-1}, seems, at first sight, large. It was derived from the most probable value of the entropy deficit by assuming a cosine-form of the barrier profile; errors introduced by this assumption are unlikely to be large enough to alter V_b appreciably. Moreover, completely independent support for a large potential-energy barrier in methyl nitrite comes from recent nuclear magnetic resonance work by Piette, Ray, and Ogg.[17] These workers and, independently, Phillips, Looney, and Spaeth,[18] examined the spectra of a number of nitrite esters. Barrier heights V_b of *ca.* 10,000 cal. mole^{-1} are found [18] for *n*-propyl, *iso*propyl, *n*-butyl, *iso*butyl, and *iso*pentyl nitrites by assuming the frequency of isomer interconversion to be adequately represented by a simple "absolute" rate equation $\nu = (kT/h) \exp(-V_b/RT)$. The same interpretation of the data [17] for methyl and ethyl nitrites leads to a similar value of V_b. This simple approach is unlikely to be seriously in error.

In nitrous acid, the existence of a *cis*- and a *trans*-form has been deduced [11] from

[16] Partington, "An Advanced Treatise on Physical Chemistry," Vol. I, page xli, Longmans, Green & Co., London, 1949.
[17] Piette, Ray, and Ogg, *J. Chem. Phys.*, 1957, **26**, 1341.
[18] Phillips, Looney, and Spaeth, *J. Molec. Spectroscopy*, 1957, **1**, 35.

infrared and ultraviolet spectroscopy; Jones, Badger, and Moore [11] infer that the *trans*-form is more stable than the *cis*- by 500 cal. mole^{-1} and that the barrier height is some 12 kcal. mole^{-1} above the lower minimum. A normal co-ordinate treatment by Palm,[11] with the assumption of a symmetrical two-fold potential function, also leads to barriers of between 10 and 14 kcal. mole^{-1}. In nitric acid there are identical pairs of potential maxima and minima; barrier heights between them of from 9 to 10 kcal. mole^{-1} have been deduced by Cohn, Ingold, and Poole [12] from spectroscopy and calorimetry.

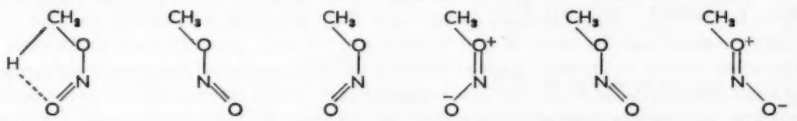
Methyl nitrate, $CH_3{\cdot}O{\cdot}NO_2$, offers an exception to this universal possession of potential barriers. The standard entropy of gaseous methyl nitrate relative to that at absolute zero can be calculated [15] from its structure and vibration frequencies. An experimental value is available from the calorimetric work of Gray and Smith [19] and recent latent heat data.[20] There is no entropy "deficit," and hence no appreciable barrier to free rotation.

No mention has yet been made of a barrier to free rotation of the methyl group. If such a barrier existed it would contribute to the entropy deficit and, as can be seen from the annexed table, if it were as high as 12 kcal. mole^{-1}, it would account for the whole deficit ($S_b = 2{\cdot}6$ cal. deg.$^{-1}$ mole^{-1}).

Postulated barrier (kcal. mole^{-1}) to free rotation of CH_3 about C–O bond	1	2	3	6	9	12
Entropy deficit (cal. deg.$^{-1}$ mole^{-1})	0·3	0·8	1·3	2·1	2·5	2·7

The reasons for its neglect are considered in the next section when the origin of the barrier to rotation is discussed. For the present it may suffice to remark that the barrier to N=O rotation derived here is not so high as to be unusual or to need supplementing by restricted CH_3 rotation.

The Origin of the Barrier to Free Rotation.—Rogowski,[8] who was the first to postulate the occurrence of methyl nitrite in *cis*- and *trans*-forms, concluded that at room temperature the *cis*-form predominated. Tarte,[1,3] and Wagner,[4] whose spectroscopic work confirmed the existence of isomers, also revealed the varying isomer ratio at different temperatures. Tarte and Wagner assumed that the form whose abundance diminished with increasing temperature was the *cis*-form. For all the primary nitrites (from ethyl upwards) this is confirmed by recent [17,18] work. Haszeldine and Mattinson [2] confirmed and extended Tarte's work. All these workers [1-4] agreed that the *cis*-forms of primary nitrites, and of methyl nitrite in particular, owed their stability to hydrogen bonding, *i.e.*, represented the *cis*- and the *trans*-isomer of methyl nitrite by (I) and (II). This explanation, although



(I) (II) (III) (IV) (V) (VI)

superficially attractive, leads to several difficulties. First, it offers no reason why a *trans*-form should be stable: if the only influence stabilizing the *cis*-form of a primary nitrite is the hydrogen bond, the *trans*-form should be much less stable. But nuclear magnetic resonance measurements on five primary nitrites (*n*-propyl, *n*- and *iso*-butyl, *n*- and *iso*-pentyl) show that the isomer ratios vary so little between $-100°$ and $+20°$ that the enthalpy increase for the isomerization *cis* ⟶ *trans* is very small; the average value is 130 cal. mole^{-1}. Secondly, hydrogen bonding implies strongly restricted rotation of the methyl group, which is not found. Thirdly, the nuclear magnetic resonance measurements on methyl and ethyl nitrites and on the five nitrites listed above fail to reveal any differentiation between the two hydrogen atoms of the sort which would arise if one of them took part in hydrogen-bond formation. For these general reasons, hydrogen-bonding is rejected as the principal factor in *cis-trans*-isomerism of all the primary nitrites.

[19] Gray and Smith, *J.*, 1953, 2380.
[20] Gray and Pratt, *J.*, 1957, 2163.

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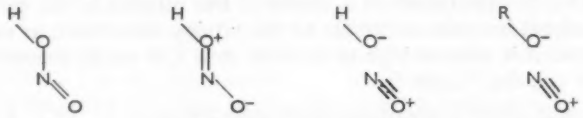
It is finally disposed of in the case of methyl nitrite by the recent nuclear magnetic resonance work. This reveals that, although in general at low temperatures the *cis*-form of the primary nitrites $R{\cdot}CH_2{\cdot}ONO$ is the more abundant, in methyl nitrite the *trans*-form predominates. At $-100°$ the *trans* : *cis* ratio is 3·4 : 1.

The most satisfactory interpretation [17,18] of the situation is in terms of partial double-bond character of the $CH_3{\cdot}O{-}NO$ link. Such an explanation has already been applied [18] to isomerism in the substituted amides and nitrosamines, and it may be made with equal validity here for the nitrite esters. Formulæ (III) and (IV) describe *cis*-methyl nitrite, and (V) and (VI) *trans*-. Such a description, by ascribing the resistance to rotation to double-bond character, permits isomers to have very little enthalpy difference and yet have a high potential barrier between them, a fact which the hydrogen-bond interpretation could not explain.* It is noteworthy that Jones, Badger, and Moore [11] reached the



(VII) (VIII) (IX) (X)

same conclusions about nitrous acid. They found that the *trans*-form predominated (*trans* : *cis* = 2·5 : 1 at 25°) and was more stable (ΔH) by 500 cal mole^{-1}. They wrote three canonical forms (VII—IX) for the *trans*-form, invoking (IX) to account for the superior stability of *trans*-nitrous acid.

In view of the excellent nitrosating power of both nitrous acid and alkyl nitrites, "no-bond" ionic structures such as (IX) and (X) are less fanciful than is common among canonical forms.

Appendix

Relative Abundance of cis- *and* trans-*Isomers in the Alkyl Nitrites.*—Three methods have been used to make inferences about the abundance ratio: electron diffraction, nuclear magnetic resonance spectroscopy, and optical (infrared, ultraviolet, and Raman) spectroscopy.

The electron-diffraction data [8] refer only to methyl nitrite. They were obtained in 1941—2 before the introduction of rotating-sector methods and their precision leaves much to be desired. Nevertheless, historically they were the first results on this system and they revealed the presence of two isomers even if they gave an inaccurate ratio.

The most recent technique, high resolution nuclear magnetic resonance spectroscopy, is the most helpful so far.[17,18] At low temperatures, when the rate of *cis–trans*-isomerization is low, the nuclear magnetic resonance spectra show well-separated peaks attributable to the proton resonances of the two isomers: the relative abundances are in the ratio of the integrated intensities. At higher temperatures, when the peaks coalesce, the relative abundances can be determined from the position of the single, unresolved maximum by assuming the frequency shift corresponding to it to be the molar average of the separate constituents. Two sets of magnetic resonance data are available. One deals with methyl, ethyl, and *n*-propyl nitrites,[17] the other with *n*- and *iso*-propyl, *n*- and *iso*-butyl, and *iso*pentyl nitrites.[18] They are in excellent accord with one another and each requires only the correct assignment of the peaks to its own isomer. Assignment made on different bases by the two sets of workers agrees both internally and with the optical results [1-3] for ethyl and all higher primary nitrites: for methyl nitrite, nuclear magnetic resonance spectroscopy reveals that, in the liquid at low temperatures, it is the *trans*-isomer which predominates.

* Ingold (personal communication) points out that this interpretation helps to explain why there is no effective barrier in methyl nitrate though there is one in nitric acid. Palm also concludes that partial double-bond character contributes to the high barrier.

Optical spectroscopy,[1-4] mainly infrared absorption, provides the third method. The vibration spectra are well enough resolved for pairs of bands ascribable to isomers to be distinguished and peak heights or, in favourable cases, integrated absorption bands can be compared. Two problems remain: not only must the bands be correctly assigned to *cis*- and *trans*-, but in order that relative abundances may be obtained from the optical

TABLE 5. *The relative stability and abundance of* cis- *and* trans-*alkyl nitrites.*

NMR = High resolution proton magnetic resonance spectroscopy; IR = Infrared (vibrational) absorption spectroscopy. L = liquid; G = gas.

Nitrite	Temperature (°c) and state	*cis* : *trans* ratio	How obtained	Ref.
	Nitrous acid			
HO·NO	25 G	0·4	Calc. ΔS; meas. ΔH	11
	Methyl nitrite			
CH_3·O·NO	−60 L	0·29	NMR integrated intensities	17
	21 L	~1	NMR mean frequency	17
	~20 G	~4	Electron diffraction	8
	23 G	(1·01)	IR optical density *	1
	Primary saturated nitrites			
C_2H_5·O·NO	F. p. L	~2·8	NMR integrated intensities	17
	21 L	~1	NMR mean frequency	17
n-C_3H_7·O·NO	F. p. L	~2	NMR integrated intensities	17
	−100 L	2·0	NMR integrated intensities	18
	20 L	1·8	NMR mean frequency	18
n-C_4H_9·O·NO	−100 L	1·8	NMR integrated intensities	18
	20 L	1·7	NMR mean frequency	18
	23 G	(0·30)	IR optical density *	1
iso-C_4H_9·O·NO	−100 L	2·3	NMR integrated intensities	18
	20 L	2·2	NMR mean frequency	18
	23 G	(0·29)	IR optical density *	1
iso-C_5H_{11}·O·NO	−100 L	1·7	NMR integrated intensity	18
	20 L	1·3	NMR mean frequency	18
	23 G	(0·29)	IR optical density *	1
	Primary unsaturated nitrites			
CH_2=CH·CH_2·O·NO	23 G	(0·36)	IR optical density *	1
C_6H_5·CH_2·O·NO	23 G	(0·32)	IR optical density *	1
	Primary dinitrites			
ON·O·$[C_2H_4]_4$·O·NO	−100 L	1·6	NMR integrated intensities	18
	20 L	1·2	NMR mean frequency	18
	Secondary nitrites			
iso-C_3H_7·O·NO	−100 L	0·13	NMR integrated intensity	18
	20 L	~0·13	NMR mean frequency	18
	23 G	(0·17)	IR optical density *	1
sec.-C_4H_9·O·NO	23 G	(0·14)	IR optical density *	1
sec.-C_5H_{11}·O·NO	23 G	(0·1)	IR optical density *	1
cyclo-C_5H_9·O·NO	23 G	(0·21)	IR optical density *	1
cyclo-C_6H_{11}·O·NO	23 G	(0·11)	IR optical density *	1
	Tertiary nitrites			
tert.-C_4H_9·O·NO	23 G	(~0·03)	IR optical density *	1
tert.-C_5H_{11}·O·NO	23 G	(~0·02)	IR optical density *	1

* These figures in parentheses are optical density ratios, D_{cis}/D_{trans}, for the N=O stretching frequency. To convert them into abundance ratios it is necessary to divide by the infrared absorption coefficient ratio $r = k_{cis}/k_{trans}$. Approximate abundance ratios can be found by using a mean value of $\bar{r} \simeq 0{\cdot}4$.

densities the infrared absorption coefficients must be determined. It is, of course, unlikely that they will differ widely from *cis*- to *trans*- and a wide variation of optical density may be taken to imply a large abundance ratio.[1,3] In this way, the predominance of *trans*-forms of the secondary nitrites and the virtual absence of *cis*-forms in the tertiary nitrites has been inferred. When both optical density data and abundance ratios from nuclear magnetic

resonance are known, ratios of infrared absorption coefficients can be determined. These ratios do not vary greatly. Thus it may be possible, without great error, to use a mean value of absorption-coefficient ratio in conjunction with optical density ratios of other nitrites to estimate the abundances of their isomers.

The three direct methods described here have been made to derive the entries in Table 5. The general results of all the methods agree.

Thus the tertiary nitrites are almost exclusively *trans*-isomer. The secondary nitrites are largely in the *trans*-form. The primary nitrites $R{\cdot}CH_2{\cdot}O{\cdot}NO$ contain appreciable amounts of both *cis*- and *trans*- with *cis*- predominating at low temperatures. The abundances do not change rapidly with temperature, and a mean value of ΔH for the isomerization *cis* ⟶ *trans* is only 130 cal. mole^{-1}. For methyl nitrite, in the liquid state, the *trans*-form predominates at low temperatures. In the liquid and probably in the gas at room temperature the ratio is nearer unity. Nitrous acid itself shows the same features: *trans*-nitrous acid predominates; it has an enthalpy of formation lower by 500 cal. than *cis*-nitrous acid. At room temperature the ratio is about 2·5 : 1.

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School of Chemistry, University of Leeds. [*Received, February 27th,* 1958.]

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688. *Crystal Structure of a Hydrated Nickel Cyanide Ammoniate.*

By J. H. Rayner and H. M. Powell.

A structure analysis of single crystals of $Ni(CN)_2,NH_3,nH_2O$ shows a modified form of the tetragonal planar nickel complex found in the inclusion compound of benzene, $Ni(CN)_2,NH_3,C_6H_6$. The layers are puckered slightly, the angle Ni–C–N in the Ni–C–N–Ni sequence of atoms being 173°. The layers are staggered so that the projecting ammonia groups of one point towards the holes in the square networks of its neighbours. They are, therefore, packed much more closely than is possible in the benzene compound. The probable water content is represented by the formula $Ni(CN)_2,NH_3,\frac{1}{4}H_2O$. It is shown that single crystals of the tetragonal benzene compound in the presence of moisture change to this hydrate structure, the main plane of the puckered layer remaining parallel to the original layers whose axial directions also remain unchanged.

Hofmann and Höchtlen [1] state that an ammoniacal nickel cyanide solution several days after preparation deposited hopper-shaped crystals of composition $Ni(CN)_2,4H_2O$. Attempted repetitions of their experiments with solutions of the same composition gave no crystals in the first few weeks, but one solution in the course of a year deposited a hydrated nickel cyanide–ammonia complex. This consisted of small crystals in spherical aggregates about 2 mm. in diameter and some single crystals about 0·25 mm. long.

Results

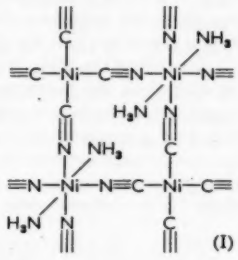
The crystals are orthorhombic, pseudo-tetragonal bipyramids. Inter-edge angles, measured under the microscope, showed {121} as the principal faces with {001}, {010}, and {100} small. Of these {010} were rounded. There is a marked cleavage parallel to (001).

X-Ray examination was carried out by oscillating-crystal methods with copper radiation filtered through nickel. Intensities of reflexions were determined from Weissenberg photographs obtained with oscillation about principal axes.

The unit cell dimensions are $a = 7{\cdot}24$, $b = 14{\cdot}32$, $c = 8{\cdot}74$ Å. Hence from the density 1·98 g./c.c. (flotation) there are eight molecules of composition $Ni(CN)_2,NH_3,nH_2O$ ($n = 0{\cdot}4$). The value of n so determined is insensitive to changes in the density. Since the value from the

[1] Hofmann and Höchtlen, *Ber.*, 1903, **36**, 1149.

analytical figures is also insensitive, a probable value of n is deduced later from the structure analysis. Absent spectra are hkl when $h + k + l$ is odd. Reflexions of type $hk0$ are absent when either h or k is odd, with the exceptions of a very weak reflexion 110 and a still weaker 130. If these reflexions, which are mentioned later, are disregarded, the space group is I*mma* or I*ma* and the first examination of the structural possibilities was limited to these groups. The unit cell dimensions are related to those of the tetragonal unit cell of the compound $Ni(CN)_2,NH_3,C_6H_6$,[2] which has $a = b = 7{\cdot}24$, $c = 8{\cdot}3$ Å. The new structure has a the same and b approximately double. From this it may be concluded that the structure contains a network similar to that in the benzene compound (I), and that its plane is perpendicular to the pseudo-tetragonal axis. This agrees with the cleavage and optical properties. The c dimension of the hydrated complex is not so simply related to that of the benzene compound. It is 8·74 Å but in this height there are twice as many $Ni(CN)_2,NH_3$ layers as in the 8·28 Å c dimension of the benzene compound.



(I)

If it is assumed that ammonia groups are attached to alternate nickel atoms as in the benzene compound the arrangement of the layers must be different. In the benzene complex ammonia groups of adjacent layers are almost in contact and only a slight contraction of the interlayer spacing would be possible if the benzene molecules were removed. But if the benzene molecules are imagined as removed and alternate layers of the remaining structure are displaced through $\frac{1}{2}a$, a large decrease in interlayer spacing is possible. Ammonia groups now (cf. Fig. 5, p. 3417) project towards the holes of the squared pattern instead of towards the other ammonia groups. This arrangement requires consistent weakness but not complete absence of some classes of X-ray reflections. For the orthorhombic cell of the hydrated complex the arrangement places the nickel atoms on a face-centred sub-cell with sides a, $\frac{1}{2}b$, c. Consequently, reflexions for which h, $k/2$, and l are neither all odd nor all even should be weak. They are observed to be so.

From this starting point the full structure was developed, through several stages of Fourier approximations and then by least-squares refinements. The nickel position being known, co-ordinates may be estimated for the other atoms of the complex consistent with the space group I*mma* and the probable bond lengths. Structure factors F_{hk0}, calculated from these co-ordinates, gave an agreement factor of 0·23. For these first calculations atomic scattering factors for carbon and nitrogen were those of the International Tables for the Determination of Crystal Structures; f_{NH_3} was taken equal to f_N and for f_{Ni} Brindley's measurements[3] for metallic nickel were used. The general correctness of the structures was shown by a Fourier synthesis of the $hk0$ structure factors. From a total of 38 observed values only six small terms of doubtful sign were omitted. All the observed peaks correspond to parts of the complex. The low agreement factor ($R = 0{\cdot}23$) and the resulting projection show that the analysis is essentially correct. The water molecule is not shown by any peak and must be hidden under the nickel atom at $0\frac{1}{2}0$. Its position at $0\frac{1}{2}z$ is a four-fold one in the space-group I*mma* and would require an ideal formula $Ni(CN)_2,NH_3,\frac{1}{2}H_2O$. When an allowance was made in structure factors for a water molecule at this place the agreement factor improved to 0·17. A second Fourier synthesis including all 38 terms gave the electron density map of Fig. 1.

Small movements of the lighter atoms did not change the signs of the structure factors, so that further refinement was undertaken by the method of difference syntheses. Fig. 2 shows a synthesis in which the coefficients are the algebraic differences between the observed and the calculated structure factors (both taken with the calculated signs). At a short distance along the b axis from the origin, there is a prominent peak. For calculation of the structure factors, ammonia groups had been assumed to lie along the c direction above and below the origin. The difference synthesis suggests that they should be moved, consistently with the symmetry, some distance along b. Depressions may be seen in the positions of the carbon and the cyanide nitrogen atoms. To correct these a temperature factor was applied to the contributions of these atoms. The scattering factor for the ammonia groups was then taken as ten times the value of J. M. Robertson's general factor for light atoms.[4] This factor is applicable to organic

[2] Rayner and Powell, *J.*, 1952, 319.
[3] Brindley, *Phil. Mag.*, 1936, **21**, 786.
[4] Robertson, *Proc. Roy. Soc.*, 1935, *A*, **150**, 106.

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structures. It has been used here since a similar treatment improved agreement in the benzene compound. This implies that the ammonia group has more freedom of movement than the CN group. The change in the co-ordinates of the ammonia nitrogen atom reduced the disagreement factor from 0·17 to 0·16. A further reduction to 0·14 resulted on application of a temperature factor $\exp\{-B(\sin\theta/\lambda)^2\}$ to the contributions of carbon and nitrogen of the CN groups. For these tightly bound atoms the low value of $B = 1{\cdot}0$ was selected. However, an increase of B to 2·0 has a negligible effect on the agreement factor. The difference synthesis with these re-calculated structure factors is shown in Fig. 3. Elimination of the large peak near the origin is evident and the depressions are in part removed.

The tilt of the NH_3–Ni–NH_3 line away from the c axis and the fact that the b axis is about 1% smaller than the corresponding distance in the benzene compound suggest that there is some slight tilt of the layers out of the (001) plane. Patterson syntheses and calculation of structure factors F_{0kl} confirm this and show that the nickel atom Ni(2) attached to four carbon atoms has a z co-ordinate approximately 0·05 and Ni(1) which is linked to four cyano- and two ammonia-nitrogen atoms has $z = 0$. For the calculation of the first set of $0kl$ structure factors ($R = 0{\cdot}27$) these Ni co-ordinates were used, and carbon and nitrogen atoms were assumed to lie on straight

FIG. 1. *Structure viewed down the c axis. To the left, electron-density map with contour interval 2·6 e/Å³ (5·2 e/Å³ for the Ni + NH_3 peak). Negative regions dotted. Atomic positions indicated by crosses and by circles in the mirror image, right half.*

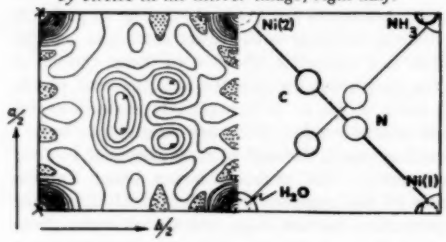


FIG. 2. F_{hk0} *difference synthesis. Crosses show atomic positions used for* $F_{calc.}$, *contour interval 0·7 e/Å². Negative contours broken. Zero contour omitted.*

lines joining two nickel atoms. Quantities used in these calculations of F_{0kl} were: f_{Ni}, from Brindley;[3] f_C and f_N of CN from International Tables modified by a temperature factor with $B = 2{\cdot}0$; f_{NH_3} = ten times Robertson's general factor,[4] the z parameter for Ni(2) = 0·047. The resulting Fourier synthesis showed, however, that the carbon atoms did not lie on the line joining Ni(1) to Ni(2) but had the same z co-ordinate as Ni(2). A difference synthesis led to some changes of parameters and an agreement factor of 0·21.

Further refinement of this structure involves a mixed set of variables, some atomic positions, some temperature factors, and one parameter to take account of a deficiency in water content of the structure. For this refinement a least-squares method was found convenient. The rigid planar structure of the complex suggests that an anisotropic temperature factor ought to be introduced especially for the nickel atoms. In the least-squares method as first applied, only the temperature factors of the nickel atoms and the Ni(2) z parameter were considered; the process gave $\Delta B_y = -0{\cdot}34$, $\Delta B_z = +1{\cdot}09$, $\Delta z = -0{\cdot}001$, where the structure factor is represented by:

$$F_{(0kl)} = \sum_j f_j \exp\{-B_{jy}Y^2 - B_{jz}Z^2\} \cos 2\pi ky \cos 2\pi lz$$

The negative value of ΔB_y would require the nickel atoms to be more firmly held in this direction than in metallic nickel. Although this might be so it was considered sufficient to use $B_y = 0$; B_z was taken = 1·0 and $\Delta z = -0{\cdot}001$, hence $z = 0{\cdot}046$, and the structure factors, recalculated on this basis, gave an improved value for R of 0·18. A least-squares process was then applied to the y and z co-ordinates of all atoms. Eight parameters are involved, yz for C, N, and N of NH_3, and z only for Ni(2) and H_2O. The modified co-ordinates deduced from this resulted in an agreement factor $R = 0{\cdot}136$. A least-squares method then applied to the x and y co-ordinates reduced the agreement factor for $F(hk0)$'s from 0·14 to 0·114. The F synthesis computed as a result of these refinements is shown as Fig. 4.

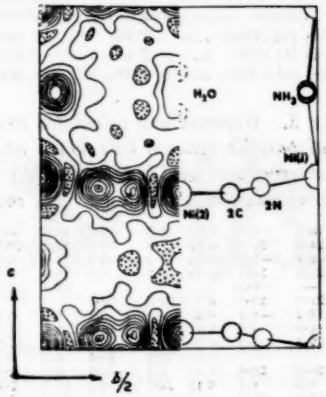
Chemical analysis and the density both suggested that the crystals contained less than $\frac{1}{2}H_2O$ per nickel atom. If the composition is $Ni(CN)_2,NH_3,nH_2O$, and there is a randomly distributed set of vacant spaces, then for $0kl$ we have:

$$\partial F/\partial n = f_{H_2O} \cos 2\pi ky \cos 2\pi lz$$

and a similar equation holds for F_{hk0}. Up to this point n had been taken as 0·5 as required by the symmetry of space group I*mma*. By applying these equations the values for Δn were obtained. F_{0kl} gave $\Delta n = -0{\cdot}18$, $\sigma = 0{\cdot}06$; F_{hk0} gave $\Delta n = -0{\cdot}26$, $\sigma = 0{\cdot}02$ (σ = standard deviation). From this it was concluded that the most probable value of n was $\frac{1}{4}$. Structure factors were recalculated with this value and for F_{hk0} the agreement factor R was reduced from 0·114 to 0·085. This value of n, giving the water content, leads to a calculated density of 1·94 g./c.c. (observed 1·98 g./c.c.). Nast [5] has state that in analyses of the substance the value of n was never found greater than 0·37. The symmetry of space group I*mma* requires at least four equivalent water molecules and hence $n = 0{\cdot}5$. The deficiency could explain the weak reflexions 110 and 130 observed although incompatible with this space group. This would involve some departure from a random distribution of vacant spaces which in turn might lead to some modification of the value deduced above for n. Aynsley and Campbell [6] give a composition corresponding to a monohydrate for material prepared by the decomposition of $Ni(CN)_2,4NH_3,2H_2O$, and a similar analysis for a blue gelatinous precipitate obtained by Hofmann and Höchtlen's method.[1] These materials may not be the same as the crystalline substance described here.

FIG. 3. *Second difference synthesis. Crosses show revised atomic positions. Contour intervals as Fig. 2.*

FIG. 4. *The structure viewed along the a axis. To the left electron-density map with contour interval 2 e/Å³ (4 e/Å³ for Ni atoms). Negative regions dotted. Atomic positions indicated by crosses and by circles in the mirror image, right half.*



The co-ordinates found for the atoms in the two projections do not completely determine the positions of the atoms in three dimensions. The three-dimensional co-ordinates for the two types of nickel atom and for the carbon and nitrogen atoms of the cyanide groups follow directly from the two projections, but the ammonia groups could be at either (0, 0·028, 0·764; $\frac{1}{2}$, 0·028, 0·736) or (0, 0·028, 0·736; $\frac{1}{2}$, 0·028, 0·764) with in each case the other six related positions of type I*mma* (h). In the first set they would be at 2·10 Å from Ni(1) atoms and in the second at 2·34 Å. The Ni–NH_3 distance found in the benzene compound was 2·06 Å and the nickel–nitrogen distance found by Driel and Verweel [7] in $K_2Ca[Ni(NO_2)_6]$ was 2·15 ± 0·03 Å. It is therefore probable that the first set of positions is correct.

A similar difficulty arises in the case of the water molecules but it is complicated both by the

[5] R. Nast, personal communication.
[6] Aynsley and Campbell, *J.*, 1957, 4137.
[7] Driel and Verweel, *Z. Krist.*, 1936, **95**, 308.

deficiency in water content already mentioned and by the uncertainty whether the water molecules are distributed evenly over four positions as is required by the space group I*mma*, or are concentrated at two of these positions giving a structure of lower symmetry. The two projections could be explained if the space group is I*mma* and the water molecules have the co-ordinates (0, ¼, 0·809; ½, ¼, 0·691; 0, ¾, 0·191; ½, ¾, 0·309) or (½, ¼, 0·809; 0, ¼, 0·691; ½, ¾, 0·191; 0, ¾, 0·309). The first of these positions is 3·10 Å and the second 2·07 Å from Ni(2). The non-bonded radius of nickel is about 2·0 Å and so the expected distance between a nickel atom and water molecule not bonded to it is about 3 Å. If the complex is to take the same form as in the benzene compound with Ni(2) in square planar co-ordination and forming no

TABLE 1. *Final atomic co-ordinates in* $Ni(CN)_2,NH_3,\frac{1}{4}H_2O$ *positions (a), etc., named as in International Tables.*

			x	*y*	*z*				*x*	*y*	*z*
4	Ni(1)	(a)	0	0	0	16	N	(j)	0·292	0·102	0·028
4	Ni(2)	(e)	¼	¼	0·046	8	NH_3	(h)	0	0·028	0·764
16	C	(j)	0·319	0·158	0·045	4	($\frac{1}{4}H_2O$)	(e)	0	¼	0·809 or 0·691

TABLE 2. *Interatomic distances in* $Ni(CN)_2,NH_3,\frac{1}{4}H_2O$.

Atoms	Length (Å)	Standard deviation (Å)	Atoms	Length (Å)	Standard deviation (Å)
Ni(1)–N (of NH_3) ...	2·10	0·04	C–N (of CN)	1·15	0·05
Ni(1)–N (of CN) ...	2·11	0·04	Ni(2)–H_2O	3·10 or 2·07	0·06
Ni(2)–C (of CN) ...	1·86	0·04	H_2O–NH_3	3·22, 3·19	—

TABLE 3. *Observed and calculated structure factors. (hk0 and 0kl listed separately. Minor disparities between 0k0 which appear twice arise because two zones of reflexions were observed and used independently.)*

F_{hk0} hk	Obs.	Calc.	F_{hk0} hk	Obs.	Calc.	F_{0kl} kl	Obs.	Calc.	F_{0kl} kl	Obs.	Calc.	F_{0kl} kl	Obs.	Calc.	F_{0kl} kl	Obs.	Calc.
0 2	10·8	9·3	4 10	2·9	2·7	10 0	—	0·5	18 2	4·6	4·7	5 5	3·2	−2·1	0 8	4·2	1·6
0 4	24·5	23·7	4 12	17·0	14·5	12 0	22·2	23·6				7 5	14·8	15·6	2 8	11·5	15·9
0 6	2·9	−1·6	4 14	4·0	−4·3	14 0	6·1	−6·4	1 3	32·1	−29·3	9 5	6·2	−6·1	4 8	4·7	4·2
0 8	31·1	35·1	4 16	8·2	8·5	16 0	5·3	4·5	3 3	1·4	1·5	11 5	11·1	11·6	6 8	7·6	8·8
0 10	—	0·5				18 0	2·7	2·8	5 3	12·1	−11·2	13 5	10·5	−9·6	8 8	3·2	2·2
0 12	22·0	23·6	6 0	29·5	29·7				7 3	10·1	7·2	15 5	4·6	4·2	10 8	8·0	11·0
0 14	6·2	−6·4	6 2	—	0	1 1	6·4	−7·8	9 3	14·2	−13·0				12 8	1·2	0·9
0 16	4·9	4·5	6 4	18·8	18·2	3 1	4·5	5·0	11 3	7·8	6·8	0 6	9·9	9·4			
0 18	2·5	2·8	6 6	5·3	5·3	5 1	10·2	7·1	13 3	12·4	−11·5	2 6	9·6	10·0	1 9	5·4	−7·7
			6 8	16·6	15·9	7 1	9·8	9·7	15 3	3·4	2·7	4 6	3·9	4·0	3 9	0·8	−0·3
2 0	26·3	26·4	6 10	3·4	−4·6	9 1	2·8	2·3	17 3	0·7	−0·9	6 6	8·4	5·8	5 9	1·5	−0·1
2 2	8·6	6·1	6 12	14·8	14·1	11 1	5·9	6·4				8 6	8·4	8·1	7 9	4·6	6·2
2 4	58·0	61·1				13 1	1·7	−1·4	0 4	41·0	43·9	10 6	10·2	11·2	9 9	1·2	−0·6
2 6	5·0	5·1	8 0	9·0	8·2	15 1	2·6	1·9	2 4	16·7	16·6	12 6	7·1	6·3	11 9	1·9	2·7
2 8	28·5	25·0	8 2	2·3	2·3	17 1	1·7	0·3	4 4	16·7	15·2	14 6	5·5	5·3			
2 10	4·9	−5·5	8 4	18·9	19·1				6 4	8·7	7·0				0 10	2·9	−4·4
2 12	15·0	13·7	8 6	1·7	−1·7	0 2	47·9	58·7	8 4	20·2	18·2	1 7	14·4	−15·9	2 10	5·6	8·6
2 14	1·6	1·3	8 8	10·6	10·4	2 2	7·3	−5·0	10 4	8·3	8·0	3 7	1·1	−0·5	4 10	2·2	2·2
2 16	16·7	16·7				4 2	3·1	5·5	12 4	14·4	12·6	5 7	4·0	−4·0	6 10	3·8	4·9
			F_{0kl} kl			6 2	1·5	−1·6	14 4	1·0	0·1	7 7	6·1	6·2	8 10	1·2	0·4
4 0	40·0	41·4				8 2	25·7	25·6	16 4	3·6	3·2	9 7	6·9	−6·6			
4 2	7·5	6·1	2 0	9·7	9·3	10 2	6·2	6·1				11 7	5·0	4·3	1 11	1·6	−1·4
4 4	32·0	28·1	4 0	23·8	23·7	12 2	23·3	23·0	1 5	21·8	−23·9	13 7	7·9	−8·6	3 11	1·9	−3·1
4 6	3·9	−3·2	6 0	2·1	−1·6	14 2	1·2	0·1	3 5	6·0	7·0						
4 8	28·8	24·4	8 0	35·0	35·1	16 2	7·0	7·2									

fifth bond, then the second set of positions is too close to nickel atoms. If, as is possible, the water is co-ordinated to nickel, the second set provides sites for it at a reasonable distance.

The numerical results of the structure analysis are collected in Tables 1—3. The standard deviations in Table 2 are from the least-squares refinement.

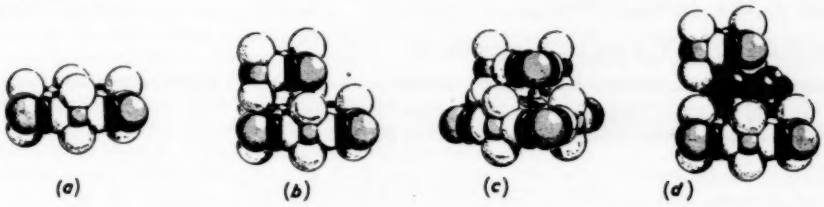
DISCUSSION

The layers of the complex found in the structure are a slightly distorted form of those in the benzene compound. The bond lengths in the two are very similar. The nickel–carbon bond, 1·86, is slightly longer than that in the benzene compound, 1·76 Å, and so approaches nearer to a single bond. The carbon–nitrogen distance, 1·15 (cf. 1·22 Å), appears to be nearer to a triple bond value than in the benzene compound but its significance is doubtful in view of the estimated errors.

The planar arrangement of four bonds at right angles around Ni(2) and the regular octahedral bonds around Ni(1) are preserved but the layers as a whole are puckered (Fig. 4). This puckering appears to be brought about entirely by a departure of the Ni–C–N–Ni sequence of atoms from linearity at the carbon atom. The angle Ni–C–N is 173°. The Ni(2) atom and its four attached carbon atoms lie in a plane parallel to (001), *i.e.*, parallel to the mean plane of the complex. The octahedron of Ni(1) is tilted so that the plane of the four cyanide nitrogen atoms makes an angle of seven degrees to (001), and the bonds of the ammonia groups are tilted in the (100) plane through a corresponding angle away from the *c* axis.

In the benzene complex the presence of molecules between the layers contributes to the stability. This is apparent from the very close packing of the structure as a whole. By contrast any structure consisting of parallel layers of the complex only is bound to be an open one owing to the manner in which the projecting ammonia groups hold the layers apart in certain places and thus produce unoccupied spaces in others. In the present structure, the layers are arranged as closely as possible with the projections of one fitting into the spaces of the other. This may be seen from Fig. 5(*c*). Although this brings the layers much closer together than in the benzene complex, it leaves considerable space, part

FIG. 5. (*a*) *Approximate perspective drawing of part of the nickel cyanide ammonia complex layer. Nitrogen atoms white; carbon, black; nickel, dotted.* (*b*) *One method of interleaving layers.* (*c*) *Interleaving of layers as adopted in the hydrate.* (*d*) *Superposition of layers as in* (*a*), *showing the included benzene molecules of the* $Ni(CN)_2.NH_3.C_6H_6$ *structure. Note the greater inter-layer spacing than with* (*c*).



of which is occupied by water molecules. Puckering of the layers shows that the van der Waals interaction is, in these giant molecules, great enough to cause this distortion from normal bond-angles.

The elucidation of this crystal structure makes it possible to explain some observations made on the benzene complex. Crystals of this compound used for *X*-ray photography were found at the end of a month to be opaque. This change did not take place when the crystals were kept in a desiccator for the same length of time. *X*-Ray photographs of crystals which had not been preserved in a desiccator showed a number of diffuse spots in addition to the normal diffraction pattern. These occurred in positions corresponding to the strongest reflexions in the diffraction pattern of the hydrate. In particular, when an undecomposed crystal of the benzene complex had given a Weissenberg photograph (zero layer) on rotation about [100], and was then photographed again after exposure to the air for a few weeks, the original diffraction pattern had superposed on it a number of diffuse spots which coincided with the positions of diffraction spots that would be given by a single crystal of the hydrate rotating about its *a* axis. The *a*,*b*,*c* of the hydrate coincide with *a*,*a*′,*c* of the tetragonal benzene compound. From this it is concluded that the decomposition, which occurs in the presence of water vapour, takes place by the escape of benzene and the displacement and puckering of layers into the positions corresponding to the hydrate structure. In this process the mean plane of the puckered layers remains parallel to the original plane of the complex in the benzene compound, and the orthorhombic axes *a* and *b* in the plane emerge parallel to the *a* and *b* tetragonal axes of the original crystal. The decomposition is observed as a white surface opacity. The observed

X-ray reflexions on the Weissenberg photographs which are elongated in the direction of movement of the film suggest that the decomposed mass consists of crystallites in nearly parallel orientation, with axial directions distributed over a few degrees. It has recently been reported [8] that on removal of benzene from the complex by evacuation the cell dimensions show a continuous variation. This is presumed to be a different mode of decomposition of the compound.

The present results agree best with the formula $Ni(CN)_2,NH_3,\frac{1}{4}H_2O$, but do not remove uncertainties regarding other reported hydrates. Materials analysed by Nast [5] ($0{\cdot}37H_2O$) and by Cambi, Cagnass, and Tremolada [9] ($0{\cdot}2H_2O$) could be the same as that described here. Aynsley, Campbell, and Dodd [8] mention that their dehydrated monohydrate reabsorbs water from the atmosphere, but that the product resulting from removal of benzene from the clathrate $Ni(CN)_2,NH_3,C_6H_6$ shows no tendency to absorb water, although, as shown above, water can be absorbed while benzene is removed. It is already clear that layers of the complex may be arranged relatively to each other in more than one way, and that "single" crystals may have complex intermediate structures. It is possible therefore that a number of hydrates, perhaps including non-stoicheiometric forms, may exist.

Experimental.—Hydrated nickel cyanide–ammonia complex. The original substance was crystallised during the course of a year as described above [Found: C, 18·5; H, 2·9; N, 30·6. Calc. for $Ni(CN)_2,NH_3,\frac{1}{4}H_2O$: C, 18·2; H, 2·7; N, 31·8%]. A few crystals from this batch were added as seeds to a similar solution which then deposited a compound in about a month (Found: C, 18·5; H, 2·7; N, 31·0%).

We thank Mr. D. V. Jones for drawing Fig. 5.

CHEMICAL CRYSTALLOGRAPHY LABORATORY, OXFORD. [*Received, March 7th*, 1958.]

[8] Aynsley, Campbell, and Dodd, *Proc. Chem. Soc.*, 1957, 210.
[9] Cambi, Cagnass, and Tremoloda, *Gazzetta*, 1934, **64**, 758.

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689. *Ion-exchange Properties of Cellulose Phosphate.*

By A. J. HEAD, N. F. KEMBER, R. P. MILLER, and R. A. WELLS.

The ion-exchange properties of cellulose phosphate prepared by the urea–phosphoric acid method have been investigated. This material has been shown to possess a high affinity for certain cations, principally Th^{4+}, Ti^{4+}, U^{4+}, Ce^{4+}, Fe^{3+}, ZrO^{2+}, and UO_2^{2+}, which are adsorbed from 4N-acid. The influence of the preparative conditions and structure of the ester on its ion-exchange properties is described and discussed.

A PHOSPHORIC ester of cellulose was prepared in connection with the flameproofing of textile fabrics by Coppick and Hall.[1] Its value as a cation-exchange material was later pointed out by workers at the Southern Regional Research Laboratory, U.S.A.,[2,3] and it has been used for the precipitation of proteins.[4] We have examined [5] the use in inorganic chromatography of paper prepared from such material by W. & R. Balston Ltd. The cation-exchange behaviour of cellulose phosphate was significantly different from that of sulphonic acid resins; in particular, ferric ions were strongly adsorbed, and were not eluted from columns of this material by 0·5N-hydrochloric acid.

[1] Coppick and Hall, "Flameproofing Textile Fabrics," Reinhold Publ. Corp., New York, 1947, pp. 179 *et seq.*
[2] Jurgens, Reid, and Guthrie, *Textile Res. J.*, 1948, **18**, 42.
[3] Hoffpauir and Guthrie, *ibid.*, 1950, **20**, 617.
[4] *Idem, J. Biol. Chem.*, 1949, **178**, 207.
[5] For a preliminary communication see Kember and Wells, *Nature*, 1955, **175**, 572.

W. & R. Balston Ltd. have shown [6] that Coppick and Hall's method of preparation, which consisted of impregnating cellulose with a solution of urea and phosphoric acid followed by heating at 130—170° and yielded a material containing up to 5% of phosphorus, can be extended to give more highly substituted cellulose, fibrous in character, insoluble in acid and alkali, and having an ion-exchange capacity up to 10 mequiv./g. This compares favourably in capacity with convential ion-exchange resins, yet has the high reaction rate associated with the hydrophilic cellulose matrix.[7]

Cellulose phosphate has also been prepared by treating cellulose with phosphorus oxychloride and sodium hydroxide [8] or pyridine.[9] The latter reaction is accompanied by degradation of the cellulose and some chlorination of hydroxyl groups.[10] The work now described was carried out with material prepared by the reaction of urea and phosphoric acid, the principal product from which is believed to be monoammonium monocellulose hydrogen phosphate.[10,11,12] Its physical nature permits packing in columns through which aqueous solutions can be passed, so it can therefore be used similarly to conventional ion-exchangers.

Experimental

Preparation of Cellulose Phosphate.—Strips (*ca.* 9 g.) of wood-pulp cellulose (99% α-cellulose) were steeped in a solution of urea (50% w/w) and orthophosphoric acid (18% w/w), and the excess of liquor uniformly expressed until the required uptake had been obtained. Our experiments were restricted to a liquor : cellulose ratio of 3·0 (w/w), corresponding to a mean degree of substitution of 0·9. Higher values can be reached but the reproducibility of such samples was somewhat less satisfactory. The strips were heated (" cured ") in an oven (30 cm. cube), electrically heated to 130°, through which air preheated to the same temperature was vigorously forced (22 air changes per min.). After the required period the treated cellulose was plunged into water, macerated mechanically into fibres (where necessary), filtered off, washed with water, and spin-dried in a basket centrifuge. The moisture content was determined by heating the product for 4 hr. at 110° and the phosphorus content was measured spectrophotometrically by the vanadomolybdate method after wet oxidation.

Stability of Cellulose Phosphate in Acids and Alkalis.—The extent of hydrolysis of cellulose phosphate in 2N-sulphuric acid, 10% aqueous ammonium carbonate, 10% aqueous sodium carbonate, and N-sodium hydroxide was measured at room temperature (*ca.* 20°). The material used was " cured " for 2·5 hr. and then " conditioned " as below for 3 days; it contained 9·7% of phosphorus. The ester (5 g.) was shaken with the reagent (200 ml.), and 10 ml. portions were withdrawn at intervals. These were evaporated, organic matter was oxidised, and the solutions were analysed for phosphorus. The results (Fig. 1) show that alkaline hydrolysis is rapidly suppressed by the phosphate ions produced. Acid hydrolysis can be largely prevented by adding a greater excess of phosphate; thus the phosphorus content of the ester was lowered to 9·3% after 6 hours' shaking with 2N-sulphuric or -nitric acid, but remained at 9·7% in 2N-sulphuric acid containing 20% (w/v) of sodium dihydrogen phosphate after the same time. Phosphorus analyses refer to the monoammonium form of the ester which, unlike the H-form, can be dried at 110° without appreciable decomposition.

Adsorption of Metal Ions by Cellulose Phosphate.—The product obtained after 1 hour's curing (1 g.) was converted into the H-form with N-sulphuric acid in a column (2 cm. int. diam.) and a 0·1M-solution of the appropriate metal ion (500 ml.) in sulphuric acid solution (except for lanthanum and bismuth for which solubility considerations necessitated use of hydrochloric and nitric acid respectively) passed through at 2 ml. per min. at room temperature (*ca.* 20°). The column was washed with acid at the same concentration and the cellulose phosphate analysed for the metal after wet oxidation.

Adsorption of Thorium by Cellulose Phosphate.—To prevent the complications due to

[6] Balston, unpublished information.
[7] Guthrie, *Ind. Eng. Chem.*, 1952, **44**, 2187.
[8] Peterson and Sober, *J. Amer. Chem. Soc.*, 1956, **78**, 751.
[9] Reid and Mazzeno, *Ind. Eng. Chem.*, 1949, **41**, 2828.
[10] Reid, Mazzeno, and Buras, *ibid.*, p. 2831.
[11] Nuessle, Ford, Hall, and Lippert, *Textile Res. J.*, 1956, **26**, 32.
[12] Davis, Findlay, and Rogers, *J. Text. Inst.*, 1949, **40**, T 839.

hydrolysis of the ester, the adsorption of thorium was investigated with a solution containing 7 g. of ThO_2 per l. and 2·5 g. of P_2O_5 per l. in 4N-sulphuric acid. This solution (300 ml.) was passed at 3 ml. per min. through columns (2 cm. int. diam.) containing the appropriate sample of cellulose phosphate (2 g. based on the dry monoammonium form) after conversion into the H-form with 2N-sulphuric acid. After adsorption it was convenient to wash the column with 2N-sulphuric acid, water, and 2N-ammonia and to elute the thorium as the carbonato-complex with 100 ml. of 10% ammonium carbonate solution followed by 100 ml. of water. Thorium was readily precipitated as hydrated oxide by boiling the eluate, and after acidification was determined by precipitation as oxalate.

Acidification of boiled eluates never yielded clear solutions and it was always necessary to filter off a small quantity of a gelatinous precipitate, which readily coagulated on boiling. The dried solid had the following analysis: H, 2·7; O, 22·6; P, 8·3; Th, 32·5%. "*Thorium cellulose phosphate*," $C_{12}H_{18}O_{14}P_2Th$, requires H, 2·5; O, 20·2; P, 8·7; Th, 32·6%. The oxygen content was calculated as that available after formation of thorium pyrophosphate, the probable residue in the determination (Unterzaucher's method). It was impossible to obtain a reliable microanalysis for carbon and the individual results for hydrogen varied widely. This is attributed to the difficulty of completely burning carbonaceous matter occluded in the pyrophosphate glass—the combustion residues were always black (see below).

Titration of Cellulose Phosphate.—The ester (*ca.* 300 mg.) was converted into the H-form and washed free from excess of mineral acid before being transferred with water (50 ml.) to a titration cell containing calomel and glass electrodes and a mechanical stirrer, and through which nitrogen could be passed. The vigorously stirred suspension was titrated against 0·1N-sodium hydroxide; steady pH readings were obtained within a few minutes, even above pH 9 where the rate of reaction was slowest. After completion of the titration both the pulp and the liquid were analysed for phosphorus; these results show that approximately 6% of the total phosphorus was hydrolysed into the liquid phase during the process.

Results and Discussion

Table 1 shows that certain ions (particularly Fe^{3+}, Ce^{4+}, UO_2^{2+}, U^{4+}, Th^{4+}, ZrO^{2+}, and Ti^{4+}) are strongly adsorbed from N-acid, in marked contrast to the behaviour on sulphonic acid resins. To elute these metals reagents are needed which form strong complexes with them. Thus thorium and uranyl are quantitatively eluted with 10% ammonium carbonate solution. Qualitatively, this reagent also removes uranous ion; acetone–hydrochloric acid can be used for iron, and ammonium fluoride solution for zirconium. Table 1

Table 1. *Adsorption (atoms of metal per atom of phosphorus) on cellulose phosphate*

Ion	Adsorption			Maximum calc. value (normal valency)
	N-Acid	pH 2	pH 3	
Al^{3+}	0	1·00	—	0·67
Bi^{3+}	0·10	—	—	0·67
Ce^{4+}	0·52	*	—	0·50
Cu^{2+}	0	0·13	—	1·00
Fe^{3+}	0·31	0·38	—	1·00
Fe^{3+}	1·17	0·80	—	0·67
La^{3+}	0·06	0·25	—	0·67
Mg^{2+}	0	0·23	—	1·00
Mn^{2+}	0	—	0·43	1·00
Th^{4+}	0·46	0·73	0·91	0·50
Ti^{4+}	0·73	*	—	0·50
U^{4+}	0·24	—	—	0·50
UO_2^{2+}	0·43	0·66	0·82	1·00
Zn^{2+}	0·06	0·20	—	1·00
ZrO^{2+}	1·18	*	—	1·00

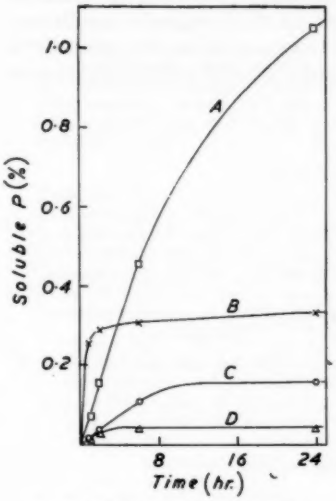
* A precipitate is formed at this pH.

indicates that in some instances the maximum theoretical adsorption, calculated from the phosphorus content of the exchanger and the normal valency of the adsorbed ion, is exceeded, indicating that complex ions of lower valency are involved. At pH 3 the adsorption of

thorium is accompanied by sulphate such that the Th : SO_4 ratio was 0·96, suggesting that $ThSO_4^{2+}$ or $Th(HSO_4)^{3+}$ is the species adsorbed.[13]

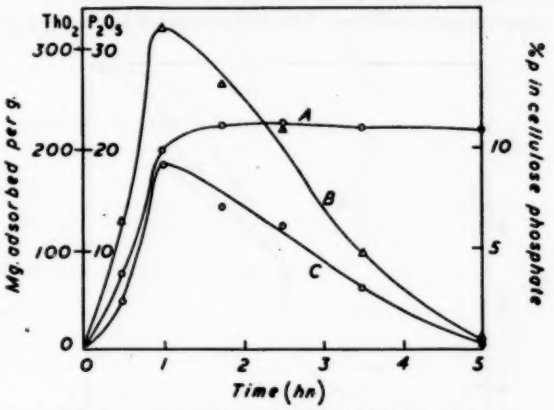
To study the variation in the ion-exchange properties of cellulose phosphate in acid solution with preparative conditions, the adsorption of thorium from 4N-sulphuric acid under standard conditions was measured. To minimise acid hydrolysis of the ester, phosphate ions were added to the thorium solution, but material eluted from these columns contained appreciable quantities of phosphate (P_2O_5 : ThO_2 ~1 : 20). This could not

FIG. 1. *Hydrolysis of cellulose phosphate by acid and alkali.*



A, 2N-H_2SO_4. *B*, N-NaOH. *C*, 10% *Aq.* Na_2CO_3. *D*, 10% *Aq.* $(NH_4)_2CO_3$.

FIG. 2. *Influence of curing time.*



A, P *content*. *B*, ThO_2 *adsorbed*. *C*, P_2O_5 *adsorbed*.

have arisen from the ion-exchange material itself since the thorium capacity did not diminish after several successive adsorption–elution cycles. The proportion of phosphate in the eluate increased as more was added to the original thorium solution (Table 2), suggesting that part of the thorium is adsorbed as a cationic species of thorium phosphate.

TABLE 2.

Solution applied to column	Product eluted: ThO_2 (mg. per g. of cellulose phosphate)	Product eluted: P_2O_5 (mg. per g. of cellulose phosphate)	$100(P_2O_5/ThO_2)$
0·01M-$Th(SO_4)_2$ in 2N-H_2SO_4	373	10·5	2·8
0·01M-$Th(SO_4)_2$ in 2N-H_2SO_4, 0·013M with respect to PO_4	390	20·0	5·1
0·01M-$Th(SO_4)_2$ in 2N-H_2SO_4, 0·20M with respect to PO_4	426	40·0	9·4

Thorium ions are known to form complexes with phosphate in sulphuric acid solution in which the existence of species such as $Th(H_2PO_4)_2^{2+}$ and $ThH_2PO_4^{3+}$ have been postulated,[14] and from which well-defined substances corresponding to $Th(HPO_4)SO_4$ and $[Th(H_2PO_4)_3]_2SO_4$ crystallised.[15] Further evidence for the adsorption of an ion of lower valency is provided by the increased thorium capacity as the proportion of phosphate

[13] Schulz and Herak, *Croatian Chem. Acta*, 1957, **29**, 49.
[14] Zebroski, Alter, and Heumann, *J. Amer. Chem. Soc.*, 1951, **73**, 5646.
[15] d'Ans and Dawihl, *Z. anorg. Chem.*, 1929, **178**, 252.

in the solution is increased. That cellulose phosphate possesses no anion-exchange properties whereby phosphate ions could be adsorbed was demonstrated by eluting a column through which neutral and acid solutions of sodium phosphate had been passed. No phosphate was detected in the eluate.

The thorium present as the acid-insoluble fraction of the eluates amounted to 1·3% of the total quantity adsorbed. This substance is insoluble in 10% mineral acids but dissolves in 10% aqueous ammonium carbonate. It seems probable that this is the thorium salt of cellulose phosphate, which has been degraded to a low degree of polymerisation and become soluble in ammonium carbonate.

Preliminary experiments indicated that the ion-exchange properties of cellulose phosphate, particularly in acid solution, are very dependent on the preparative conditions. The experimental variables were therefore studied. The composition of the phosphorylating reagent used was that recommended by Hoffpauir and Guthrie,[3] and contained urea

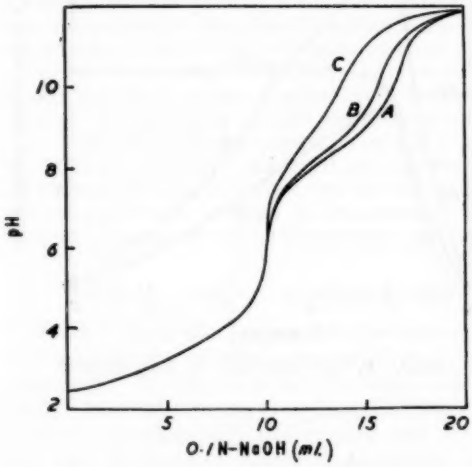


FIG. 3. *Titration curves of cellulose phosphate.*

Curing for (*A*) 1·0, (*B*) 2·5, (*C*) 5·0 *hr.*

(4 mol.) and phosphoric acid (1 mol.). Attempts to lower the molar ratio to 2 : 1 or 1 : 1 resulted in considerable charring during curing. This process was effectively carried out at 130° in a forced-draught oven (at 140° reaction was faster but less reproducible).

The effects of varying the curing time are shown in Table 3 and Fig. 2. The quantity of phosphate present in the eluates from these adsorption tests closely paralleled the thorium capacity, thus providing further evidence for cationic thorium phosphate. Short curing gives material which readily disperses in water to a white slimy pulp which retains a considerable amount of water after spin-drying (moisture contents of these materials were moderately reproducible). After longer curing the product was hard, brittle, and cream-coloured, and was broken into fibres only after vigorous mechanical treatment to give material with a low moisture content after spin-drying. The physical character of "overcured" cellulose phosphate would be an advantage in ion-exchange practice since such samples have less resistance to the flow: the flow rate of water was 30 times greater through columns prepared from material cured for 3·5 hr. than from that cured for 1·0 hr.

By analogy with the variations in the water-regain values of ion-exchange resins these results suggest that curing causes cross-linking. Indeed slow drying is known to cause wet cellulose to become horny, which is ascribed to cross-linking of the fibrils by development of crystalline regions.[16]

[16] Spurlin, "Cellulose and Cellulose Derivatives," Interscience Publ. Inc., New York, 1954, p. 696.

Contrary to the findings of Reid *et al.*[10] who stated that the urea–phosphoric acid method afforded only the primary ester, we have found by alkali-titration that even after 1 hour's curing, and before all the phosphorylating reagent had reacted, 32% of the phosphoric acid groups were diesterified. The proportion of cross-linking through phosphoric acid groups increases with curing time, as shown in Fig. 3 and Table 3. Although the most overcured sample showed negligible capacity for thorium in acid solution, its capacity for sodium ions in alkaline solution was unchanged and good agreement was

TABLE 3.

Curing time (hr.)	1·0	2·5	5·0
As prepared:			
P content (%)	9·88	11·2	10·9
g. of water per g. of dry ester	3·5	0·95	0·55
% of phosphoric acid groups disubstituted	32	41	57
ThO_2 capacity (mg. of ThO_2 per g. of ester)	319	223	10
P_2O_5 capacity (mg. of P_2O_5 per g. of ester) *	18·4	12·2	0·6
P_2O_5/ThO_2 (%)	5·8	5·5	6·0
Stored as suspension of H *form for* 3 *days*:			
P content (%)	8·24	9·63	9·42
g. of water per g. of dry ester	7·0	2·6	1·2
% of phosphoric acid groups diesterified	15	20	34
ThO_2 capacity (mg. of ThO_2 per g. of ester)	274	299	101
P_2O_5 capacity (mg. of P_2O_5 per g. of ester) *	3·5	2·0	0·4
P_2O_5/ThO_2 (%)	1·3	0·7	0·4
Stored as suspension of H *form for* 7 *days*:			
P content (%)	7·92	9·28	9·24
g. of water per g. of dry ester	8·9	2·7	1·4
% of phosphoric acid groups diesterified	9	—	25
ThO_2 capacity (mg. of ThO_2 per g. of ester)	240	268	221
P_2O_5 capacity (mg. of P_2O_5 per g. of ester) *	2·4	0·6	0·0
P_2O_5/ThO_2 (%)	1·0	0·2	0·0

* Phosphorus adsorbed with thorium as cationic complex.

obtained between the phosphorus content of the sample titrated (21·2 mg.) and that calculated from the first end-point (21·4 mg.). Similar proof that every phosphorus atom in cellulose phosphate carries an acidic group was found when the sample heated for 1 hr. was titrated (Found: P, 28·5 mg. Calc.: P, 28·9 mg.). If cellulose phosphate is converted into the H-form and washed free from excess of mineral acid, and an aqueous suspension is kept at room temperature for several days, some hydrolysis of ester linkages occurs. The hydrolysis of primary groups is suppressed by the phosphoric acid produced and the secondary groups are thus preferentially attacked. The removal of cross-linking is demonstrated by the results of titrations carried out on samples which had been stored as aqueous suspension of the H-form (" conditioned ") for 3 and 7 days (Table 3). These provide minimum values for cross-linking since some hydrolysis of these linkages probably occurs during titration. Further proof that this conditioning destroys cross-linking is given by the higher moisture contents.

Table 3 shows that by reducing the amount of cross-linking the thorium capacity of overcured samples can be restored, although if " conditioning " is excessively prolonged this effect will be outweighed by the reduction in capacity caused by hydrolysis. Although a sample cured for 2·5 hr. and stored for 3 days has a similar thorium capacity to one cured for 1 hr. without any subsequent treatment, and the latter contains a higher proportion of diesterified phosphoric acid groups, yet the physical properties of the former sample (lower moisture content and a nine-fold greater flow rate of liquids through columns of the material) indicate that some other form of cross-linking resists conditioning. This residual cross-linking is probably that caused by heating of wet cellulose (cf. above) although it may also be connected with the fact that the N : P ratio of overcured material

exceeds the theoretical ratio of 1·0 required for the monoammonium salt of cellulose phosphate and found for the sample cured for 0·5 hr. (observed value 1·08; N by Kjeldahl method). Thus this ratio reached 1·21 for overcured samples and after acid-washing was still 0·27. A high N : P ratio has been observed previously to be a feature of more severe curing conditions and to be accompanied by some loss of ion-exchange properties (as measured by the persistence of flameproofing qualities, after soaking of the NH_4-form in calcium chloride solution; flameproofing has been shown to be associated with the NH_4- or H-form of cellulose phosphate but not with the calcium or other metal-cation form).[17] Side reactions leading to the formation of the diamide Cell·O·P(O)$(NH_2)_2$ and cellulose carbamate Cell·O·CO·NH_2 have been postulated,[1,11] although the former is now excluded by the finding that every phosphorus atom carries exchangeable hydrogen.

Table 3 also shows that the adsorption of thorium as cationic phosphate is considerably reduced on conditioned cellulose phosphate and reaches zero on a sample cured for 5 hr. and

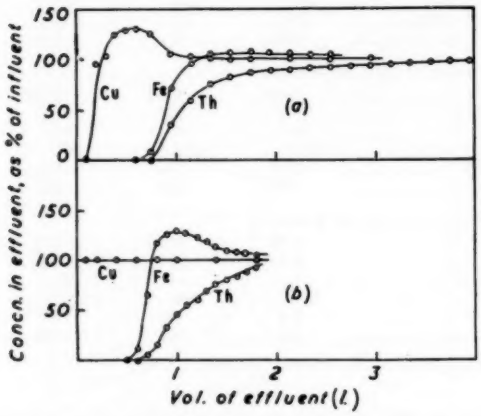


FIG. 4. *Break-through curves for adsorption of copper, iron, and thorium from* (*a*) 0·1N- *and* (*b*) N-H_2SO_4.

conditioned for 7 days. However no simple relation exists between the proportion of diesterified phosphoric acid and either the thorium capacity or the amount of adsorbed phosphate. The exact structure of any sample of ester depends, not only on its phosphorus content and the proportion of diesterified phosphoric acid, but also on the extent of the other mode of cross-linking, which it is not possible to measure. If it is required to reduce the adsorption of phosphate or if practical considerations make reduced resistance to flow of liquid desirable, the use of cellulose phosphate which has been somewhat overcured and subsequently conditioned is an advantage.

The relative affinities of Cu^{2+}, Fe^{3+}, and Th^{4+} were demonstrated by passing a solution containing 5 mequiv./l. of each of the ions in 0·1N-sulphuric acid through a column of cellulose phosphate prepared with short curing time. The breakthrough curves (Fig. 4) show the relative affinity order $Th^{4+} > Fe^{3+} > Cu^{2+}$; in N-sulphuric acid (Fig. 4) the affinity order was the same, but with increasing selectivity for Th^{4+}. Thus at the end of the experiment the quantities of metal adsorbed were in the equivalent proportion of Th/Fe = 2·8 from 0·1N- and Th/Fe = 3·8 from N-acid solution. In neither case was copper found.

The different affinity of cellulose phosphate for various cations enables several chromatographic separations to be carried out. Thus bismuth and lead are both adsorbed on the top of a column of cellulose phosphate in the H-form from 0·1N-nitric acid, and lead is quantitatively eluted free from bismuth with N-nitric acid. Complete recovery of bismuth is obtained by elution as the anionic complex formed with N-hydrochloric acid.

[17] Little, ref. 1, pp. 199—203.

Separations in neutral solutions have also been achieved. Mixtures of copper with cadmium, cobalt, or nickel are adsorbed on the top of ion-exchange columns in the sodium form. Elution with N-magnesium chloride quantitatively removes the second component, leaving copper on the column, from which it can be completely recovered by using N-hydrochloric acid. These separations are extensions of those already briefly described for paper strips; [5] either under- or over-cured and stored cellulose phosphate may be used.

There are several references to ion-exchange materials carrying phosphonate [18-20] or phosphate groups [20,21] but the affinity of cellulose phosphate for certain cations in strongly acid solution is remarkable. Kennedy *et al.*[20,22] investigated the behaviour of polymers from allyl phosphate and phosphonate and report an order of affinities Th^{4+}, $U^{4+} > UO_2^{2+}$, $Fe^{3+} > La^{3+} > H^+ > Cu^{2+}$, Co^{2+}, $Ca^{2+} > Na^+$, which agrees with our results for cellulose phosphate. These experiments were carried out at acidities not exceeding 0·2N, although the limitation which prevented their extension to higher acidity appeared to be one of reaction rate rather than displacement of the equilibrium. It is significant that it is those cations with phosphates precipitated below pH 2 which are most strongly adsorbed, although the acidity at which adsorption occurs on cellulose phosphate is considerably higher than that which permits precipitation from solution. Kennedy has pointed out that the bonds between, *e.g.*, Th^{4+}, Fe^{3+}, UO_2^{2+} and phosphate or phosphonate groups are at least partially covalent. The marked dependence of ion-exchange properties in acid solution on the structure of the exchange material supports the belief that directional, covalent bonds are formed between resin sites and adsorbed ions. The greater flexibility of a cellulose matrix which is not cross-linked permits the correct stereochemical configuration for compound formation. Similarly, under the standard conditions of testing, no thorium is adsorbed on to the commercial resins Duolite C-60 and C-61, which possess respectively phosphonous and phosphonic acid groups attached to a hydrocarbon matrix. A somewhat analogous situation to the adsorption of cations in acid solution occurs at the other end of the pH scale in the strong adsorption of aurocyanide ions on weakly basic resins which would be expected to have no anion-exchange capacity in strongly alkaline media.[23] This has been attributed to ion-pair formation between the resin sites and the highly polarisable aurocyanide ions.[24] The greater polarisability of the phosphate group than of the sulphate group [25] probably results in bonds of greater covalent character on exchange material carrying the former function than on resins of sulphonic acid type. The order of polarisability phosphate > water > sulphate has been used to explain the inversion of the affinity order of the alkali metals on phosphonic acid exchange materials.[19]

We acknowledge the co-operation of the staff of W. & R. Balston, Ltd., who provided many of the early samples of cellulose phosphate. We thank Miss A. M. Berkley and Mrs. D. F. Johnson for assistance with the experimental work and Miss M. Corner for microanalyses. This paper is published by permission of the Director of the Chemical Research Laboratory and of the United Kingdom Atomic Energy Authority.

RADIOCHEMICAL GROUP, D.S.I.R. CHEMICAL RESEARCH LABORATORY,
TEDDINGTON, MIDDLESEX. [*Received, March 19th*, 1958.]

[18] Walsh, Beck, and Toy, *J. Amer. Chem. Soc.*, 1956, **78**, 4455; U.S.P. 2,525,247, 2,764,561—3.
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[22] Kennedy and Davies, *Chem. and Ind.*, 1956, 378.
[23] Aveston, Everest, Kember, and Wells, *J. Appl. Chem.*, 1958, **8**, 77.
[24] Aveston, Everest, and Wells, *J.*, 1958, 231.
[25] Teunissen and de Jong, *Kolloid-Beih.*, 1938, **48**, 33.

690. *New Methods of preparing Polonium Metal.*

By K. W. Bagnall, P. S. Robinson, and M. A. A. Stewart.

Polonium metal has been prepared by the action of aqueous ammonia on polonium hydroxide and of anhydrous liquid ammonia on the hydroxide and some other polonium compounds. It can also be prepared by reducing polonium hydroxide with hydrazine, hydroxylamine, or sodium dithionite in alkaline solution and polonium tetrachloride with stannous chloride, titanous chloride, or sodium dithionite in hydrochloric acid.

The usual methods of obtaining the metal from polonium compounds on the milligram scale have been by deposition on a supporting metal [1] or chemical precipitation,[2] followed by vacuum sublimation. Early trace-level work had indicated that reduction, presumably to the element, could be brought about by many reagents including hydrazine [3] (from alkaline solution) and stannous chloride [4] or titanous chloride [3] (from acid solution). These and other reducing agents have now been applied to polonium compounds on the milligram scale.

Quadrivalent polonium hydroxide in aqueous potassium hydroxide is reduced rapidly at laboratory temperatures by hydrazine, hydroxylamine, and the dithionite ion, and the black product is definitely the metal. On trace evidence sodium dithionite had been said [5] to give sodium polonide under a blanket of hydrogen at higher temperatures, but this would be difficult to confirm on the milligram scale owing to the intensely oxidising conditions associated with the α-bombardment from curie-level sources. By contrast, sulphite reduces alkaline quadrivalent polonium hydroxide only to the bivalent state, which rapidly reverts to the quadrivalent condition when the reagent is consumed.

In dilute hydrochloric acid, polonium tetrachloride is reduced by stannous chloride, titanous chloride, and sodium dithionite, in every instance to the metal, though in the last the product is contaminated with sulphur. Whether produced from acid or alkaline media, the metal is present in both the α- and the β-form, with the former predominating. This mixture of allotropes is consistent with recent findings [6] which indicate that the two forms co-exist over the temperature range 18—54°.

Strangely, and contrary to earlier reports [3] on the behaviour of trace polonium with formaldehyde in the presence of alkali, neither formic acid nor formaldehyde reduces quadrivalent polonium in either acids or alkalis.

A new route to the metal has been found as a result of our early observation that polonium hydroxide, left in contact with moderately concentrated aqueous ammonia, turns black. The product behaved like the metal in being converted into the quadrivalent hydroxide by prolonged treatment with aqueous potassium hydroxide. Analysis showed nitrogen to be absent and *X*-ray powder photography identified it as the mixture of the low- and the high-temperature form of the metal (70% of α-Po, 30% of β-Po) found previously. This reduction, however, took place only when the concentration of the ammonia was above 5N, and had an induction period which decreased as the concentration of the reagent increased. Furthermore, its inception was invariably at the centre of the particles of hydroxide, whereupon it spread outwards rapidly. With anhydrous liquid ammonia instead of the aqueous solution, the reaction appeared to be immediate.

Because of these interesting features this reaction was examined more closely. First it was shown that substituted ammonias also brought about the reduction and that the

[1] Bagnall and D'Eye, *J.*, 1954, 4295.
[2] Bagnall and Robertson, *J.*, 1957, 1044.
[3] Guillot and Haissinsky, *Bull. Soc. chim. France*, 1935, **2**, 239.
[4] Marckwald, *Ber.*, 1902, **35**, 4239.
[5] Chlopin and Samartzewa, *Compt. rend. Acad. Sci. U.R.S.S.*, 1934, **4**, 433.
[6] Goode, *J. Chem. Phys.*, 1957, **26**, 1269.

induction period progressively increased in the order $EtNH_2 < Et_2NH < Et_4N^+ < Et_4N{\cdot}OH$. The rate of reduction was always slower than with aqueous ammonia. The reaction went to completion with the first two, though it required 20 min. for liquid diethylamine, whereas the last two failed to reduce more than a small fraction of the polonium hydroxide even after 40 min. Secondly, it was shown that a previous irradiation of the aqueous ammonia by α-particles did not alter the characteristics of the reaction.

Neither aqueous ammonia nor a substituted ammonia behaves as reducing agent under the conditions of these experiments, and the phenomena must therefore be related to the α-radiation from the polonium. In evidence of this, tellurous acid, which is unaffected by aqueous ammonia, was rapidly reduced to tellurium when a suspension of polonium metal in aqueous ammonia was added to it.

It is not easy to decide on the reducing species produced by the α-irradiation, but the fact that 15M-ammonium hydroxide, which had been irradiated for 15 min. by α-particles from a curie source of polonium metal, failed to behave differently from the unirradiated reagent suggested that the reduction could not be ascribed to the radiolytic production of such stable compounds as hydrazine or hydroxylamine. Both of these reduce polonium compounds immediately in alkaline media. The nitrogen–hydrogen bond is not strong and hydrogen atoms may be expected from α-particle bombardment. Their life would be short in this medium but they seem to be the most probable reducing agent. They would be produced in decreasing proportions by a corresponding irradiation in passing from liquid ammonia to liquid diethylamine, in the order in which the rates of reduction fall. On these premises, reaction with triethylamine and tetraethylammonium hydroxide would not be expected and the slight slow reaction shown by these compounds may be due to adventitious, incompletely substituted ammonias, possibly formed by the α-bombardment. It is certainly significant that effective reduction takes place as long as the compound has a hydrogen bonded to a nitrogen atom.

Further experiments were carried out in which an aqueous suspension of polonium hydroxide was saturated with hydrogen, but no reduction was observed after 15 hr.: this may well be due to the low solubility of hydrogen in water and the consequent very low probability of a fruitful collision of an α-particle and a hydrogen molecule. It is also clear that the radiolysis of water and of the hydroxyl ion does not contribute to the reduction.

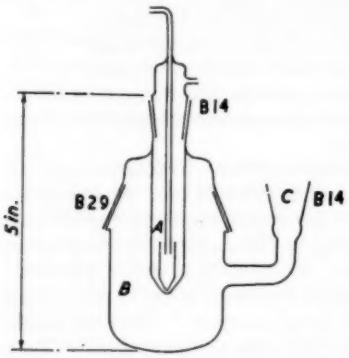
Atomic nitrogen was ruled out as an active agent since nitrogen atoms are more likely to combine with one another than with anything else.

The induction period is shorter, the greater the concentration of ammonia in the aqueous solution and is absent with liquid ammonia, which suggests that NH_3 is the species suffering disruption. It also suggests that before any reduction becomes noticeable a specific concentration of hydrogen atoms has to be reached which is first attained at the centre of the particle of hydroxide, where the α-particle radiation is greatest. Neither lead, the product of decay, nor polonium metal itself acts as a catalyst. There is, furthermore, no ground for supposing an intermediate step in the reduction, for bivalent polonium hydroxide is very much darker than the quadrivalent compound and the only colour change in the early stages of the reaction is in the other direction, owing presumably to dilution of the gel.

The state of the hydroxide or oxide also affects the rate of reduction; a specimen of the dioxide prepared by slow oxidation at room temperature gave the same induction period as the hydroxide, whereas another specimen consisting of larger crystals prepared at 450° gave a much longer induction period. The difference is probably due to the time required for the hydration of the high-temperature material. All this suggests that the induction period is simply a measure of the rate of penetration by the ammonia which will be faster when it is as discrete molecules than when it carries attached water molecules.

It seems fairly safe to assume that the reduction is due to α-particle radiolysis and that it will be much slower, if it takes place at all, with the longer-lived isotopes ^{208}Po and

^{209}Po. When these become available, the question will be readily answered. Nevertheless the present work provides two convenient methods of obtaining polonium metal on the milligram scale; they are (*a*) the spontaneous reduction of the hydroxide in concentrated aqueous ammonia, which is probably only applicable to ^{210}Po, and (*b*) the precipitation of the metal from 2N-hydrochloric acid by titanous chloride or stannous chloride, which is effective for all isotopes.



Experimental

All the work was carried out in glove-boxes.

Reagents.—Ammonia, from ammonium chloride and calcium hydroxide, was dried over soda lime. The amines were redistilled and the appropriate-boiling fractions collected.

Reactions with Liquid Ammonia.—The apparatus shown in the Figure was devised. The polonium compound was placed in a micro-cone in *A*, which was flushed out with dry ammonia gas, and then cooled in a liquid nitrogen bath. Dry ammonia gas was then passed into *A* until the tube was approximately one-quarter full of solid ammonia. The cooling bath was then removed and the section *A* fitted into the jacket *B* which was evacuated *via* the side-arm *C*, thus converting the apparatus into a transparent vacuum flask. The excess of ammonia was finally evaporated off after admission of air to the jacket (*B*), and the micro-cone transferred to a B14 socket drawn down to an *X*-ray capillary into which the contents of the micro-cone could be tapped out under vacuum.

The authors are indebted to Dr. R. W. M. D'Eye for measuring and indexing a number of the *X*-ray films.

Atomic Energy Research Establishment, Harwell. [*Received, April 21st,* 1958.]

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691. *A Proof of the Constitution of Cassanic Acid based on its Derivation from Vouacapenic Acid.*

By F. E. King, T. J. King, and J. M. Uprichard.

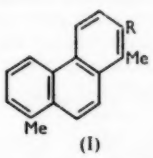
The structure attributed [1] to cassanic acid, namely, that of a perhydro-1 : 8 : 8 : 13-tetramethyl-2-phenanthrylacetic acid, has been confirmed by a partial synthesis of the acid from methyl vouacapenate.[2]

The suggested *trans*-arrangement of the A/C ring junction in vinhaticoic acid,[3] and therefore in vouacapenic acid, has been confirmed by oxidation of methyl tetradehydrovinhaticoate to a dimethyl*cyclo*hexanetricarboxylic acid of known configuration.[4]

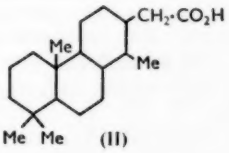
Among the well-defined class of *Erythrophleum* alkaloids,[5] which are of interest for their cardiac activity, the most extensively investigated is cassaine, $(C_{19}H_{29}O_2)\cdot CO\cdot O\cdot CH_2\cdot CH_2\cdot NMe_2$, an ester of cassaic acid, $(C_{19}H_{29}O_2)\cdot CO_2H$. Cassaic acid is an αβ-unsaturated monocarboxylic acid, the presence of a hydroxyl and of a carbonyl group accounting for the remaining oxygen atoms.[5,6] Reduction of the ethylenic

[1] Humber and Taylor, *J.*, 1955, 1044.
[2] King, Godson, and King, *J.*, 1955, 1117.
[3] King and King, *J.*, 1953, 4158.
[4] Barton and Schmeidler, *J.*, 1948, 1197; 1949, S 232.
[5] G. Dalma, "The Alkaloids," edited by Manske and Holmes, Academic Press New York, Vol. IV, p. 265.
[6] Woodward and Eastman, *J. Amer. Chem. Soc.*, 1950, **72**, 399.

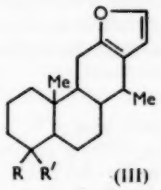
bond and removal of the alcoholic and carbonyl functions affords cassanic acid, $C_{19}H_{33}\cdot CO_2H$, and, by dehydrogenation of this acid, 1 : 2 : 8-trimethylphenanthrene ($C_{17}H_{16}$) (I; R = Me) is obtained.[7] An attempt to locate the carboxyl group by reaction with methylmagnesium iodide and dehydrogenation of the product gave a C_{20} alkylphenanthrene,[8] and in accord with the suggestion[1] that the carbonyl group in cassaic acid is extranuclear, the C_{20} hydrocarbon was identified by synthesis as 2-*iso*butyl-1 : 8-dimethylphenanthrene (I; R = $CH_2\cdot CHMe_2$). As a result of this evidence it was concluded that cassanic acid is a perhydrophenanthrylacetic acid (II).



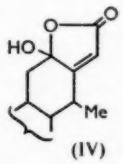
(I)



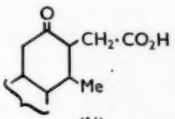
(II)



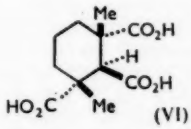
(III)



(IV)



(V)



(VI)

Although cassanic acid is thus assigned to the tricyclic diterpene series, it will be seen that structure (II) does not entirely conform to the isoprene rule because of the methyl group at position 1. In this respect it resembles the epimeric esters methyl vouacapenate and methyl vinhaticoate (III; R = Me, R′ = CO_2Me, and *vice versa*).[2,3] To see if the skeletal similarity extended also to stereochemical details, a partial synthesis of the acid (II) from one or other of the esters (III) was investigated. Perphthalic acid converted methyl vouacapenate into a hydroxylated lactone (IV; R = Me, R′ = CO_2Me), but catalytic hydrogenation of this failed, as with menthofuran.[6] Reduction under modified Clemmensen conditions[9] gave the neutral crystalline ester of acid (V), containing an isolated carbonyl group, further characterised as 2 : 4-dinitrophenylhydrazone and oxime. The acid then obtained by hydrolysis was more readily prepared by zinc–acetic acid reduction of the lactone, and related acids were similarly derived from methyl vinhaticoate and vouacapenol (III; R = Me, R′ = $CH_2\cdot OH$). These reactions, applied to vouacapenane (vinhaticane) (III; (R = R′ = Me) gave the keto-acid necessary for our synthesis.

In this series Clemmensen reduction was ineffective, and Huang-Minlon reduction gave a mixture, as, for example, with methyl 3 : 16-dioxoeburico-7 : 9(11)-dien-21-oate.[10] The methyl ester of (V; R = R′ = Me) failed to give a ketal with ethanethiol, but a crystalline product was obtained with ethanedithiol and was readily converted by Raney nickel into the required compound (II). Identity with methyl cassanate was confirmed by comparison of the infrared absorption spectra which were virtually indistinguishable. We thank Dr. B. Engels, Eidgenossische Technische Hochschule, Zürich, for generous samples of methyl cassanate. The properties of the derived dimethylcarbinol also and of the acid were similar to those recorded for the dimethylcarbinol from methyl cassanate and for cassanic acid, but direct comparison was not practicable.

The relationship of the *Erythrophleum* alkaloids to the group of diterpenes represented by vouacapenic and vinhaticoic acids is therefore firmly established and embraces the

[7] Ruzicka, Dalma, and Scott, *Helv. Chim. Acta*, 1940, **23**, 757.
[8] Ruzicka, Engel, Ronco, and Berse, *ibid.*, 1945, **28**, 1038.
[9] Fieser, Fry, and Jones, *J. Amer. Chem. Soc.*, 1939, **61**, 1852.
[10] Bowers, Halsall, and Sayers, *J.*, 1954, 3070.

whole hydrophenanthrene nucleus. However, little is definitely known of the absolute configuration of this ring-system, and although there is substantial evidence by analogy, no rigid proof of the A/C ring fusion has so far been advanced. Attempts to oxidise methyl vinhaticoate, for example, to the dimethyl*cyclo*hexanetricarboxylic acid (VI) obtained from abietic acid have so far been unsuccessful. This work has been renewed since starting the present investigation, but with methyl tetradehydrovinhaticoate, and it has been found that vigorous oxidation with nitric acid does in fact give the C_{11} triacid on which the stereo-structure of the abietic A/C ring junction is based. Identity of the product with the known acid was established by mixed m. p. and infrared absorption measurement. The *trans*-configuration of the A/C ring in vinhaticoic, vouacapenic, and cassanic acid and its precursors is thus determined.

Experimental

Light petroleum was of b. p. 60—80°. Optical rotations were determined for the D line in $CHCl_3$ solution at room temperature.

Perhydro-8β-methoxycarbonyl-1 : 8 : 13-trimethyl-3-oxo-2-phenanthrylacetic Acid (V; R = Me, R′ = CO_2Me).—(*a*) The permonophthalic acid oxidation product of methyl vouacapenate [2] (1·5 g.) in methanol (60 c.c.) and benzene (60 c.c.) was added to amalgamated zinc turnings (15 g.). Hydrochloric acid (30 c.c. conc. + 8 c.c. water) was added and the mixture boiled for 7 hr., a further 10 c.c. of concentrated hydrochloric acid having been added after 4 hr. The mixture was cooled, the benzene layer collected, and the aqueous layer exhausted with ether. The combined extracts were evaporated, to give a gum (1·3 g.) which crystallised from aqueous methanol in needles (0·95 g.), m. p. 116—120°, raised to 119—120° by crystallisation from light petroleum, of the *methyl ester*, [α] +10° (*c* 1·1) (Found: C, 69·5; H, 8·8. $C_{22}H_{34}O_5$ requires C, 69·8; H, 9·1%). The derived 2 : 4-*dinitrophenylhydrazone* formed golden-yellow needles (from methanol–ethyl acetate), m. p. 234—236° (Found: C, 60·1; H, 7·1; N, 10·1; OMe, 10·9. $C_{34}H_{38}O_8N_4$ requires C, 60·2; H, 6·9; N, 10·1; 2OMe, 11·1%). The *oxime*, prepared in pyridine, crystallised from aqueous methanol in rods, m. p. 107—108° (Found: N, 3·6. $C_{22}H_{35}O_5N$ requires N, 3·6%). The above ester with 10% ethanolic sodium hydroxide (reflux) for 1 hr. gave the corresponding *acid* (see below) (Found: C, 69·3; H, 8·8. $C_{21}H_{32}O_5$ requires C, 69·2; H, 8·9%).

(*b*) The lactone (IV) (2·7 g.) from methyl vouacapenate, and zinc turnings (11 g.), were heated under reflux in acetic acid (80 c.c.) for 7 hr. The solution was then poured into water and extracted with ether. The product crystallised from aqueous methanol to give the acid as needles, m. p. 152—154° (1·8 g.). Further purification from light petroleum gave needles, m. p. 155—156°, [α] +7° (*c* 2·1) (Found: C, 69·1; H, 8·9%). Diazomethane afforded the ester identical with that prepared by method (*a*). The acid gave a 2 : 4-*dinitrophenylhydrazone*, golden needles, m. p. 235—236° (Found: C, 59·4; H, 6·7; N, 10·4. $C_{27}H_{36}O_8N_4$ requires C, 59·6; H, 6·7; N, 10·3%).

Perhydro-8α-methoxycarbonyl-1 : 8 : 13-trimethyl-3-oxo-2-phenanthrylacetic Acid (V; R = CO_2Me, R′ = Me).—The oxidation product (2·7 g.) of methyl vinhaticoate [3] was reduced as in (*b*) above. The crude product was initially purified through the insoluble sodium salt formed with aqueous sodium hydrogen carbonate and then crystallised from light petroleum–ethyl acetate, to give the *acid* (1·2 g.) in long flat prisms, m. p. 156—157°, [α] −9° (*c* 2·3) (Found: C, 69·4; H, 8·8%). The 2 : 4-*dinitrophenylhydrazone* was golden needles (from methanol–chloroform), m. p. 245—246° (decomp.) (Found: C, 59·3; H, 6·6%). Diazomethane yielded the *methyl ester*, rods (from aqueous methanol), m. p. 133—134° (Found: C, 69·9; H, 9·0; OMe, 15·3. $C_{23}H_{34}O_5$ requires C, 69·8; H, 9·1; 2OMe, 16·4%). The ester *dinitrophenylhydrazone* formed golden needles (from methanol), m. p. 205—206° (Found: C, 60·0; H, 6·8%), and the *ester-oxime* separated from aqueous methanol as rods, m. p. 134—135° (Found: N, 4·0%).

Perhydro-8β-hydroxymethyl-1 : 8 : 13-trimethyl-3-oxo-2-phenanthrylacetic Acid (V; R = Me, R′ = CH_2·OH).—The peracid oxidation product (2 g.) from vouacapenol,[2] reduced as above, afforded the 8β-*acetoxymethyl compound* (1·7 g.) as laths (from aqueous methanol), m. p. 175—177°, changed by recrystallisation from light petroleum–ethyl acetate to rods, m. p. 179—180° (Found: C, 69·5; H, 8·9; Ac, 11·4. $C_{22}H_{34}O_5$ requires C, 69·8; H, 9·1; 1Ac, 11·4%). The acetate gave a 2 : 4-*dinitrophenylhydrazone* as yellow needles (from methanol–chloroform),

m. p. 243—245° (decomp.) (Found: C, 60·2; H, 7·0; N, 10·4. $C_{28}H_{38}O_8N_4$ requires C, 60·3; H, 7·0; N, 10·0%). The *acetate methyl ester* formed with diazomethane crystallised from aqueous methanol as needles, m. p. 76—77° (Found: C, 70·3; H, 9·4; OMe, 7·1. $C_{23}H_{36}O_5$ requires C, 70·4; H, 9·3; 1OMe, 7·9%).

Hydrolysis of the above acetate with aqueous-methanolic 10% potassium hydroxide on the steam-bath for 1 hr. gave the derived *hydroxy-acid* as rods (from aqueous methanol), m. p. 212—213° (Found: C, 71·6; H, 9·7. $C_{20}H_{32}O_4$ requires 71·4; H, 9·6%). Diazomethane formed the *methyl ester*, rods (from aqueous methanol), m. p. 149—150° (Found: C, 72·0; H, 9·7; OMe, 9·1. $C_{21}H_{34}O_4$ requires C, 71·9; H, 9·8; 1OMe, 8·9%).

Peracid Oxidation of Vouacapenane.—Vouacapenane [2] (10 g.) in carbon tetrachloride (125 c.c.) was treated with an ethereal solution of monoperphthalic acid (18·6 g.) during 140 hr. After having been washed successively with aqueous potassium iodide, sodium thiosulphate, and water the organic layer was evaporated to a yellow gum. This was treated with boiling water (3 × 500 c.c.) and then crystallised from aqueous methanol to give pale yellow prisms (7·5 g.), m. p. 216—218° (decomp.). The pure *lactone* (IV; R = R′ = Me) was finally obtained by further crystallisation as plates, m. p. 218—220° (decomp.) (Found: C, 75·6; H, 9·6. $C_{20}H_{30}O_3$ requires C, 75·4; H, 9·5%). The lactone was characterised as the *anhydro-derivative*; obtained after 10 min. at 220—230°, this separated from aqueous methanol as short rods, m. p. 167—168° (Found: C, 79·9; H, 9·3. $C_{20}H_{28}O_2$ requires C, 80·0; H, 9·4%).

Perhydro-1 : 8 : 8 : 13-tetramethyl-3-oxo-2-phenanthrylacetic Acid (V; R = R′ = Me).—Reduction of the above lactone (4·3 g.) as previously described afforded an acetic acid solution which was evaporated to *ca.* 70 c.c. and diluted with water (20 c.c.). After 1 hr. at 0° the crystalline *keto-acid* (3·1 g.) was collected. It crystallised from aqueous methanol in hexagonal plates, m. p. 214—216° (Found: C, 74·5; H, 9·9. $C_{20}H_{32}O_3$ requires C, 74·9; H, 10·0%). The *methyl ester* (prepared with diazomethane) crystallised from aqueous methanol in rectangular plates, m. p. 94—95° (Found: C, 75·7; H, 9·9; OMe, 8·2. $C_{21}H_{34}O_3$ requires C, 75·4; H, 10·2; 1OMe, 9·3%).

Methyl Cassanate.—The above methyl ester (0·8 g.) in a mixture of ethanedithiol (6 c.c.) and ether (15 c.c.) was treated with a slow stream of hydrogen chloride for 25 min. After 15 hr. at 0° a solution of sodium carbonate was added to the mixture and the product was collected into chloroform. The solution was washed with sodium hydroxide and water, then evaporated to give the *thioketal* as colourless needles (0·74 g.; 74%), m. p. 209—211°, raised by crystallisation from ethanol–chloroform to 211—212° (Found: C, 67·7; H, 9·2; S, 15·3. $C_{23}H_{36}O_2S_2$ requires C, 67·6; H, 8·9; S, 15·7%).

The above ketal (0·7 g.) and Raney nickel (*ca.* 10 g.) were heated under reflux in ethanol for 2½ hr. Removal of the nickel and evaporation of the solvent afforded an oil which crystallised from aqueous methanol, to give the ester as plates, m. p. 48—49°, [α] +9° (*c* 1·0) (Found: C, 78·7; H, 11·4; OMe, 9·6. Calc. for $C_{21}H_{36}O_2$: C, 78·7; H, 11·3; 1OMe, 9·7%). The mixed m. p. with methyl cassanate (m. p. 44—45°, [α] +4° ± 2°) was 47—48°.

The synthetic methyl cassanate was converted with methylmagnesium iodide into the derived dimethylcarbinol which crystallised from light petroleum as needles, m. p. 134—135° (lit., 132—133°) (Found: C, 82·6; H, 12·7. Calc. for $C_{22}H_{40}O$: C, 82·4; H, 12·6%).

Hydrolysis of the ester afforded cassanic acid which sublimed at 130°/0·05 mm., to give slender prisms, m. p. 220—221°, [α] +4·7° (*c* 0·5) (lit., m. p. 224°, [α] +3° ± 2°) (Found: C, 78·4; H, 11·0. Calc. for $C_{20}H_{34}O_2$: C, 78·4; H, 11·2%).

Nitric Acid Oxidation of Methyl Tetradehydrovinhaticoate.—Methyl tetradehydrovinhaticoate [3] (2·3 g.) was gradually added to concentrated nitric acid (20 c.c.) at 70—80°, fuming nitric acid (5 c.c.) was then added, and the mixture was boiled for 15 hr. Evaporation of the solution then gave a yellow gum which crystallised from nitric acid. Further crystallisation from acetone afforded flat rectangular prisms (50 mg., 3%), m. p. 218—220° (decomp.), undepressed on being mixed with the tricarboxylic acid (VI) similarly prepared from abietic acid (Found: C, 54·4; H, 6·7. Calc. for $C_{11}H_{14}O_6$: C, 54·1; H, 6·6%).

We thank Dr. G. D. Meakins, Manchester University, and Boots Pure Drug Co. Ltd. for the determination of infrared spectra.

THE UNIVERSITY, NOTTINGHAM. [*Received, May 9th*, 1958.]

692. *Electron Impact and Molecular Dissociation. Part I. Some Steroids and Triterpenoids.*

By R. I. Reed.

The mass spectra of fragments of some steroids and triterpenoids produced by bombardment with electrons of 9—15 ev energy indicate thermal fission during introduction of the molecules into the ion-chamber. The scope and limitations of this technique are discussed, particularly for the determination of the length of the side-chain.

Experiments with 30—70 ev electrons permit study of dissociations induced by electron-impact and the spectra of cholestane, ergostane, lanost-9(11)-ene, and stigmastadiene fragments have been qualitatively interpreted.

Correlation of the ions obtained by the electron-induced dissociation with specific structural features in the molecules is of interest and importance. Previous studies, that of Beynon [1] being of particular note, have usually been directed [2] to identification of molecules by recognition of their distinctive fragmentations (cracking patterns).

The present investigation attempts to extend these methods to low-energy bombardment and to account theoretically for the principal fragments from some steroid and triterpenoid hydrocarbons.

Results

Low electron energies were generally used but in a few cases the much higher energies [3] commonly employed for the production of " cracking patterns."

The low-energy studies were carried out in order to determine molecular weights [4] and, as far as possible, the number of carbon atoms in the side-chain. The results are given in Table 1.

Table 1.

Compound	Mol. wt. (nominal mass units) Found	Calc.	Side-chain Found	Calc.
Cholestane	372	372	110	113
Ergostane	386	386	123	127
Stigmastadiene	396	396	—	—
Stigmastanone	413	414	137	141
α-Amyrin	411	410	None	None
Lanost-9(11)-ene	413	412	—	—

Table 2.

Cholestane		Ergostane		Lanost-9(11)-ene		Stigmastadiene	
Mass	Intensity	Mass	Intensity	Mass	Intensity	Mass	Intensity
372	Parent	386	Parent	412	Parent	396	Parent
357	M	371	M	397	VS	381	S
343·6	Metastable	357·4	Metastable	288	M	353	S
262	M	276	M	287	S	288	W
232	M	232	M	274	S	257	VS
217	VS	217	VS	273	M	149	M
149	S	149	S	149	M	139	M
110	W	110	W	139	M	127	M
109	S	109	S	110	W	108	W
95	S	95	S	109	S	43	VS
55	VS	55	VS	43	S		
43	VS	43	VS				

The high-energy studies were confined to lanost-9(11)-ene, stigmastadiene, cholestane, and ergostane. Table 2 lists only the most prominent peaks, roughly classified; at the

[1] Beynon, *Nature*, 1954, **174**, 735; *Mikrochem. Acta*, 1956, 437.
[2] Gilpin and McLafferty, *Analyt. Chem.*, 1957, **29**, 990.
[3] Barnard, " Modern Mass Spectrometry," Inst. Physics, London, 1953, p. 193.
[4] de Mayo and Reed, *Chem. and Ind.*, 1956, 1481.

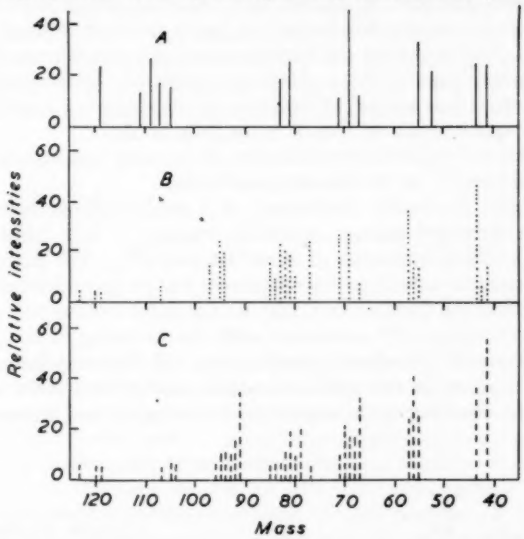
present stage, only a qualitative interpretation is justified. Agreement with published data is good. I am indebted to Mr. A. Quayle [5] for identification of the metastable peaks here reported, also for an assessment of many of the peak strengths which in general corroborate the present results.

Discussion

The observations suggest two effects: one, which predominates at low accelerating voltages, appears to be mainly a thermal effect; the other, at high electron energies, is an electron-induced dissociation.

Low-energy Spectra.—The characteristic of the thermal mechanism is that the side-chain and fragments of it are probably produced either by the heating of the sample or by a combination of this with the low-energy electron beam. This is important, for a fragment corresponding to the mass of the side-chain, or of this mass less some hydrogen atoms, should be obtained. This will be the greatest mass in a series of particles of

Fig. 1. *A, High-energy spectrum. B, Low-energy spectrum obtained by conventional methods. C, Low-energy spectrum obtained from a specimen first heated with a platinum wire.*



relatively low molecular weights corresponding to fragments of the hydrocarbon chain. In favourable cases such as those here enumerated, where the ring-skeleton is not ruptured by the conditions of experiment, confusion between the ions corresponding to fragments of the chain (terminating in a mass corresponding to the complete side-chain) and others derived from the nucleus or the nucleus plus remnants of the side-chain is unlikely. The lower series will not in general correspond to an alkyl chain of more than ten carbon atoms whereas, in the steriod and triterpenoid fields, the nucleus contains at least seventeen carbon atoms.

Under the low-energy conditions there is insufficient energy in the electron beam both to fragment and to ionise the molecule, at least to any great extent, and thus the break-down pattern from the parent hydrocarbon is rather simple. Electron-induced dissociations are of a rather low intensity, those yielding fragments formed by multiple bond-fissions being particularly weak, whilst the ions derived from the ionisation of the thermally produced particles are more abundant. Thus for cholestane the spectrum in our

[5] A. Quayle, personal communication.

experiments at low energies consists of a sparse series of peaks up to a mass of ~109 corresponding to an eight carbon fragment and then peaks of only very low intensity for masses less than 230, which correspond to the ring skeleton.

Fig. 1 shows the difference between low- and high-energy spectra for lanost-9(11)-ene in which the mass of 113 units corresponds to the complete side-chain.

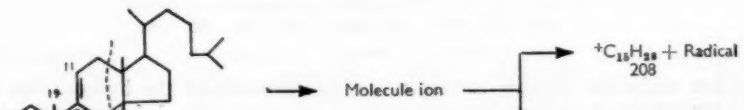
The technique described, therefore, is in favourable circumstances well suited to the determination of molecular weights on very small amounts of material, enabling a ready distinction to be made between steroids and triterpenoids. Moreover, the tetracyclic triterpenoids can be easily distinguished, by means of the side-chain estimation, from the pentacyclic members.

For substances such as α-amyrin which lack a side-chain the above pattern is much altered. There is no series corresponding to pyrolysis of the side-chain and there is virtually no spectrum until the electron-beam energy is ~18 ev, when a spectrum characteristic of the electron-induced dissociation appears. This spectrum has ions corresponding to nearly all mass-numbers for an integral number of carbon atoms with the appropriate number of hydrogen atoms. This spectrum is not further considered in this communication.

Evidence has been adduced by Brown and Gillams [6] which supports the view that molecule ions containing double-bonds tend to break preferentially at linkages β to the unsaturated centre. Studies upon the isomeric octanes [7] and nonanes [8] have also shown ready loss of a carbon chain from a quaternary centre. Additionally, the reasonable assumption is made that ions formed by breaking of one single bond will be more abundant than those which require fission of two or more such bonds.

These generalisations enable some predictions to be made concerning the main features of the " cracking-patterns " in the following molecules.

In lanost-9(11)-ene, the ready elimination of a methyl group, either the allylic $C_{(19)}$ or one of the *gem.*-dimethyl groups, would be expected. The bond-fission illustrated should also occur, yielding fragments of mass 204 and 208. The possibility of a further break-down of the radicals as well as rearrangement [9] is to be understood. The fragment of mass 204, containing the double bond, may be the more intense but, as either may gain a hydrogen, a process frequently associated with the breaking of bonds in the molecule ion,[10] or perhaps eliminate a further hydrogen atom, all that may be predicted is that an intense peak should occur in the spectrum within one or two mass units of 204—208. Alternatively, by the breaking of the allylic bonds in rings A and B masses of 287 and 125 may be obtained.



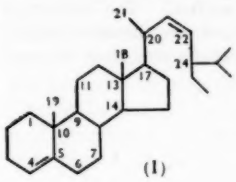
The experimental evidence agrees with this, the ion of mass 397 being the strongest in the spectrum. Moreover, ions of mass 288 and 274 are present which although relatively weak in intensity are unusually strong for fragment ions of even mass. The former may be readily interpreted as a hydrogen addition to mass 287, or by the loss of one methyl group and the entire side-chain from the original molecular ion. Mass 274

[6] Brown and Gillams, A.S.T.M. Committee E-14 on Mass Spectrometry, 2nd Annual Meeting, New Orleans, 1954.
[7] Bloom, Mohler, Lengel, and Wise, *J. Res. Nat. Bur. Stand.*, 1948, **41**, 129.
[8] Mohler, Williamson, Wise, and Wells, *ibid.*, 1950, **44**, 291.
[9] Stevenson, *Trans. Faraday Soc.*, 1953, **49**, 867.
[10] McLafferty, *Analyt. Chem.*, 1956, **28**, 306.

can be obtained from this by the further loss of a methylene group. The fairly abundant ion 149 may be obtained by further break-down of one of the larger ions.

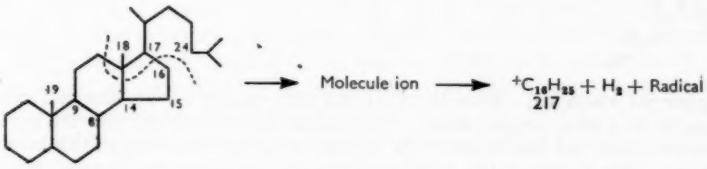
It is the occurrence of secondary reactions such as hydrogen transfer and the possibility that there is more than one origin of the fragment in the molecule which make the interpretation of fragments even of high mass difficult, and of low mass still more difficult.

The very abundant ions at masses 381, 353, 257, and 139 may be predicted for stigmastadiene (I) corresponding to the fission of the bonds at $C_{(21)}$ or $C_{(19)}$, $C_{(24)}$, and $C_{(18)}$ respectively, which is in agreement with observation except that the ion 139 corresponding to the entire side-chain is weaker than the others. Bond-fissions at positions 6 : 7 and 9 : 10 would yield rather weaker ions of masses 108 and 288 of which the latter is reduced to 149 by further loss of the side-chain. Alternatively the two-fold fission at positions 1 : 10 and 2 : 3 would give a mass of 368 which on losing the side-chain becomes 127. Peaks of moderate intensity have been observed for all of these.



(I)

The case of the homologous, saturated hydrocarbons cholestane and ergostane is more complex, as these do not possess the necessary allylic system. The most intense amongst the peaks for higher mass is 217 for both hydrocarbons, which excludes the side-chain beyond $C_{(24)}$ from the ion if it has the same source in each molecule. This has previously been interpreted as a fission which removes the side-chain and parts of rings C and D, as shown, for cholestane:



A second intense fragment common to these compounds has a mass fifteen units greater than this, which will require a quite different explanation. An alternative theory is here proposed in which the 8 : 14 bond in the molecule ion of these steranes behaves as an ethylenic double bond. No direct evidence is available as to this bond length under these conditions, but there is some chemical evidence that this is one of the more stable positions in the molecule for an ethylenic linkage, in that under certain conditions of catalytic hydrogenation, migration to this position of double bonds from positions 7 : 8 and 8 : 9 is known to occur,[11] which suggests that a more stable molecular structure is obtained by the shortening of the 8 : 14-distance.

With this assumption, the predicted fragment ions of cholestane would be 357, 262, and 110, 232, 217, 149, and 109 corresponding respectively to the elimination of the 18-methyl group and the multiple bond-fissions 6 : 7, 9 : 10, 13 : 17, and 15 : 16. The further loss of one hydrogen gives mass 109 and the elimination of a methyl group from 232 yields 217. The ion of mass 149 may be derived from the loss of the side-chain from the fragment 262. The observed results are in accordance with this. Similarly the corresponding ions, predicted and observed, of mass 371, 276, and 110, 232, 217, 149, and 109 may be obtained from ergostane. It is accordingly suggested that the above postulate provides the most economic explanation of the observed fragmentations.

The ion of mass 43 is fairly prominent in all the spectra discussed and can, moreover, be readily interpreted as due to removal of the terminal *iso*propyl group from the side-chain. However, in view of the many possibilities for producing a three-carbon fragment from such molecules, evidence of this nature is permissive rather than compelling.

[11] Rodd, "The Chemistry of Carbon Compounds," Elsevier Publ. Co., London, 1953, Vol. IIB, p. 931.

Experimental

The samples were generally analysed by volatilising the solid into the ion-chamber of a Metropolitan-Vickers M.S.2. mass-spectrometer. The electron-energy was varied from ~30 to 70 ev by using a stabilised emission current and for electron energies from 9 to 20 ev without current stabilisation. For masses up to 200 an accelerating potential of 2000 v was used which was lowered to 1000 and exceptionally 800 v for higher masses up to ~430. At this low accelerating voltage, even with the smallest practicable slit width at the collector, the resolution was poor. In all cases the spectrum was scanned by varying the field strength of the magnet.

The material was volatilised in the furnace shown in the diagram. This furnace consisted of a small copper tube some 3 mm. deep and having a 3 mm. cross-section. The bottom of the tube was closed by a sintered disc whilst the top was threaded to receive a threaded copper rod. The material under investigation was placed in the container which was then screwed on to the copper rod.

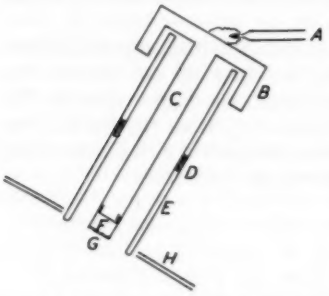


Fig. 2.

A, Micro-burner. B, Copper block on the end of the copper rod forming a gas-tight seal. C, Copper rod. D, Glass–metal seal. E, Glass inlet tube. F, Sample chamber. G, Terminal sinter. H, 2000 v, *Repeller plate of the ion chamber.*

The copper rod which had a diameter of about 2 mm. was some 9 cm. long and at the further end terminated in a small copper block. This assembly was inserted into the gas-inlet tube of the ionisation head and the copper block screwed on to the upper end of this inlet to form a gas-tight joint. The length of the total assembly was such that the sintered disc was level with the exit end of the inlet-tube in the proximity of the electron beam.

In general the samples, particularly those melting below 60°, were sufficiently volatile to provide an adequate vapour pressure for the production of a "cracking pattern." Exceptionally, heating was required which was achieved by heating the copper block by means of a gas micro-burner, the heat being conducted by the copper to the substance. The apparatus was tested on anthracene and phenanthrene, both giving identifiable mass-spectra when heated in the above furnace.

For the low-energy studies it was necessary to obtain a high-concentration of vapour because of the low efficiency of ionisation under these conditions. The samples were heated at 350—400° for 5—10 min. in a small container by gas or by a platinum wire in contact with the substance.

These compounds were then admitted to the mass-spectrometer through a sinter, which acts as a molecular leak, in the conventional manner. In order to obtain the most intense spectra possible, the machine was run at the highest sensitivity and accordingly only the relative intensities of the fragments have any significance.

I thank Professor D. H. R. Barton for advice, encouragement, and provision of samples, also Dr. P. de Mayo for the benefit of much discussion. I am also very grateful to "Shell" Research Ltd. and Mr. A. Quayle, of their Thornton Research Centre, for the provision of spectra obtained under much higher resolution than was available to me.

The University, Glasgow, W.2. [*Received, March* 3*rd*, 1958.]

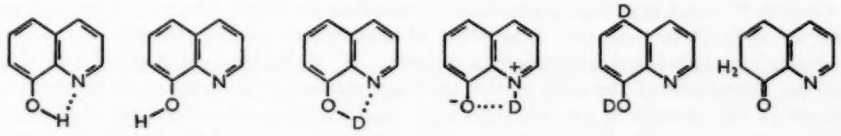
693. *Intramolecular Hydrogen Bonding in 8-Hydroxyquinolines.*

By G. M. Badger and A. G. Moritz.

The changes in O–H stretching frequencies, integrated intensities, and half-intensity band-widths of a number of substituted 8-hydroxyquinolines and *o*-benzylideneaminophenols caused by substitution have been related to Hammett's σ-constants, and are discussed in relation to the strength of the hydrogen bond. Evidence is presented for the existence of *cis-trans* isomerism in 8-hydroxyquinoline.

Although intramolecular hydrogen bonds are strongest when the ring is six-membered, bonds of significant strength are formed even when this arrangement is not possible, as for example in tropolone. 8-Hydroxyquinoline (Ia) represents another system in which intramolecular hydrogen bonding would involve a five-membered ring. Hearn, Morton, and Simpson [1] concluded from the ultraviolet spectra of 8-hydroxy- and 8-methoxyquinoline that intramolecular hydrogen bonding is absent from the former. On the other hand, many physical characteristics of 8-hydroxyquinoline indicate the presence of such a bond. Moreover, there is evidence [2] that the tautomeric equilibrium of 8-hydroxy-5-phenylazoquinoline is affected by presence of a weak intramolecular hydrogen bond. The infrared spectra of 8-hydroxyquinoline and some related compounds have therefore been examined.

The stretching vibration of an unbonded hydroxy-group appears as a strong absorption band in the 3620 cm.$^{-1}$ region. A shift of this band to lower frequencies is now accepted as a criterion for the presence of hydrogen bonding. In dilute solution in carbon tetrachloride, 8-hydroxyquinoline gave a strong band at 3416 cm.$^{-1}$, *ca.* 200 cm.$^{-1}$ lower than that expected for an unbonded hydroxyl group. The inference of weak intramolecular hydrogen bonding is confirmed by the independence of this band of concentration in the range 0·002—0·10M. At higher concentrations intermolecular hydrogen bonding becomes



(Ia) (Ib) (II) (III) (IV) (V)

possible and a diffuse band appeared at 3300—3100 cm.$^{-1}$. Even at a concentration of 1·3M, however, the intensity of the band at 3416 cm.$^{-1}$ was not significantly decreased compared with those of the C–H fundamental bands. Comparison with 1-naphthol, in which steric considerations are similar, showed that intermolecular hydrogen bonds are formed at much lower concentrations. This comparison is particularly sensitive as it has been suggested that weak intramolecular hydrogen bonds are formed in preference to stronger intermolecular bonds because of the entropy changes involved.[3]

8-Hydroxyquinoline also showed a very weak absorption band at 3672 cm.$^{-1}$, assigned to the unbonded hydroxyl vibration (*trans*-structure; Ib). Twin peaks have often been observed in the spectra of *ortho*-substituted phenols in which weak intramolecular hydrogen bonding can occur and these have similarly been interpreted in terms of *cis*- and *trans*-structures.[4] Wulf and Liddel[5] have shown that 8-hydroxyquinoline has two bands of

[1] Hearn, Morton, and Simpson, *J.*, 1951, 3318; see also Ewing and Steck, *J. Amer. Chem. Soc.*, 1946, **68**, 2181.
[2] Badger and Buttery, *J.*, 1956, 614.
[3] Jaffé, *J. Amer. Chem. Soc.*, 1957, **79**, 2373.
[4] Pauling, "Nature of the Chemical Bond," Cornell Univ. Press, New York, 1940, p. 320.
[5] Wulf and Liddel, *J. Amer. Chem. Soc.*, 1935, **57**, 1464; Hilbert, Wulf, Hendricks, and Liddel, *Nature*, 1935, **135**, 147.

weak intensity at *ca.* 6600 and 6830 cm.$^{-1}$, and this has already been interpreted as evidence for structures (Ia) and (Ib).[2]

These assignments are confirmed by deuteration of 8-hydroxyquinoline in neutral solution, the absorption bands at 3672 and 3416 cm.$^{-1}$ being replaced by a weak band at 2792 cm.$^{-1}$ and a strong twin peak at 2542 and 2526 cm.$^{-1}$. The band at 2792 cm.$^{-1}$ is probably the free OD vibration; the twin peak is tentatively assigned to Fermi resonance between the bonded OD vibration (II) and the first overtone of the 1264 cm.$^{-1}$ band. As is usual with such cases of accidental degeneracy, the intensities of the two bands are similar. In agreement with this assignment, when 8-hydroxyquinoline is deuterated in alkaline solution some C–H exchange occurs, for the resulting spectrum shows a small peak at *ca.* 2270 cm.$^{-1}$ due to an aromatic C–D stretching vibration. This spectrum [of 5(?)-deutero-8-deuteroxyquinoline (IV) shows no band near 1264 cm.$^{-1}$ and only a single bonded OD absorption at 2534 cm.$^{-1}$. The twin peak might be associated with the stretching frequencies of the O–D and $^{+}$N–D bonds (III), but the vibration limits of the two are insufficient to pass over the potential hill between the two.[6] The single peak of the hydroxy-compound would then presumably be due to the increased vibrational limits' (because of smaller mass) being above the potential hill. This interpretation seems to be precluded by Mason's [7] indication that the tautomerism to the zwitterionic structure is only slight in aqueous solvents and even less in solvents of low dielectric constant.

Séguin [8] has concluded from magnetochemical evidence that 8-hydroxyquinoline exists as the tautomer (V) to the extent of *ca.* 30% in benzene, pyridine, or quinoline, but that this is virtually absent from the solid. The spectra in benzene, in carbon tetrachloride, and in the solid do not show any carbonyl band at 1700—1680 cm.$^{-1}$, so that there is no significant proportion of structure (V). In the double-bond stretching region, however, the medium-strength band at 1628 cm.$^{-1}$ of carbon tetrachloride solutions, is very weak in the spectra of the solid; it is possible that this change is associated with the zwitterionic structure.[9] Incidentally this structure was not considered in the magnetochemical measurements.

Coulson [10] found that the various energy contributions to the strength of the hydrogen bond are difficult to evaluate. The effect of substituents on the strength of the intramolecular hydrogen bond is therefore of interest. R. M. Badger and Bauer [11] established that the magnitude of the shift of the hydroxyl stretching frequency can be used as a measure of the strength of the hydrogen bond, and Ingraham *et al.*[12] showed that a linear relation exists between the frequency shifts in substituted catechols and Hammett's σ-constants for the substituents.

The study of substituted 8-hydroxyquinolines offers additional advantages as there are six positions for substitution and the relative requirements of donor and acceptor groups in the system O–H · · · ·N might be estimated. The infrared spectra of seventeen substituted 8-hydroxyquinolines have been examined and the frequency shifts for the hydroxyl vibration are given in Table 1. The plot of ν against the σ-constants for 5-substituted 8-hydroxyquinolines (Fig. 1) clearly shows that the deviations from linearity are considerably larger than the probable errors ($\pm$1 cm.$^{-1}$ in ν; $\pm$0·06 unit in σ [13]). A linear relation has been fitted by the method of least squares and the standard deviation between observed and calculated values of ν (the error in σ being assumed to be nil) was $\pm$12·1 cm.$^{-1}$. These deviations can be regarded as evidence that the nitrogen atom is not a constant *ortho*-substituent and that there is a variable interaction between the hydroxy-group and the hetero-atom. Using the relation $\nu = \nu_0 + \rho_\nu\sigma$, Ingraham *et al.*

[6] Tsuboi, *Bull. Chem. Soc. Japan*, 1952, **25**, 385.
[7] Mason, *J.*, 1957, 5010.
[8] Séguin, *Bull. Soc. chim. France*, 1946, 566.
[9] Mason, *J.*, 1957, 4874.
[10] Coulson, *Research*, 1957, **10**, 149.
[11] Badger and Bauer, *J. Chem. Phys.*, 1937, **5**, 839.
[12] Ingraham, Corse, Bailey, and Stitt, *J. Amer. Chem. Soc.*, 1952, **74**, 2297.
[13] Hammett, "Physical Organic Chemistry," McGraw Hill, New York, 1940, p. 192.

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found a value of −12·6 for ρ_ν for the hydroxyl stretching frequencies in substituted phenols. Electron-attracting groups decrease the hydroxyl frequency in *p*-substituted phenols; but if other interactions are possible (*e.g.*, hydrogen bonding) then the looser coupling in the hydroxyl bond enables a stronger hydrogen bond to be formed and consequently a larger shift in the hydroxyl stretching frequency. The value of ρ_ν is thereby increased: our value for ρ_ν, obtained by the method of least squares, is −54·7, more than four times that for the simple phenols.

Very few results have been published on the absorption intensities of the hydroxyl group in the infrared region, although the effects of substituents in aliphatic alcohols [14] and in phenols [15] have been determined. The relation between log *A* and σ for phenols appears to be essentially linear. Moreover the half-intensity band-width shows a definite increase as the electron-attracting power of the substituent increases. The integrated intensities for the 8-hydroxyquinolines have been determined to examine the effect of substituents on an intramolecular bond, and the results are included in Table 1.

No apparent relation exists between the integrated intensity and the σ-constant, although the intensity appears to increase with the electron-attracting power of the substituent. This result is not unexpected as the substituent will also alter the electron

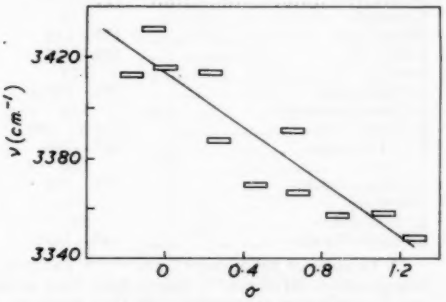
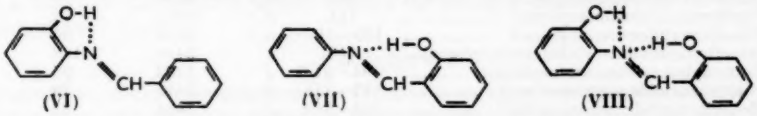


FIG. 1. *Relationship between hydroxyl stretching frequency (ν) for 5-substituted 8-hydroxyquinolines and the σ- or σ⁺-constant for the substituent.*

Rectangles are used to indicate probable errors (±1 cm.⁻¹ in ν, ±0·06 in σ).

density around the nitrogen atom, and in the discussion to follow it will be shown that the intensity is directly related to this quantity. The intensity of the hydroxyl band given by 8-hydroxy-5-phenylazoquinoline appears anomalous, and there is a similar discrepancy for the phenols [15] and anilines.[16] The high intensity does not involve the quinone phenylhydrazone tautomer (in which the OH and NH bands could be degenerate) as no carbonyl band is observed, indicating that the tautomeric equilibrium is shifted mainly towards the azo-form. The half-intensity band-widths show only minor variation with the σ-constant, but appear to increase with the electron-attracting power of the substituent.

The steric relation in *o*-benzylideneaminophenol (VI) must be almost identical with that in 8-hydroxyquinoline. In order to simplify the problem of the effect of substituents on the strength of the hydrogen bond a few benzylideneaminophenols have been examined.



(VI) (VII) (VIII)

The hydroxyl stretching frequencies and the integrated absorption intensities are given in Table 2.

Although *p*-benzylideneaminophenol has a hydroxyl stretching frequency at 3618

[14] Brown and Rogers, *J. Amer. Chem. Soc.*, 1957, **79**, 577.
[15] Stone and Thompson, *Spectrochim. Acta*, 1957, **10**, 17.
[16] Krueger and Thompson, *Proc. Roy. Soc.*, in the press.

cm.$^{-1}$, a value comparable with that for phenol itself (3610 cm.$^{-1}$), *o*-benzylideneaminophenol absorbs at 3442 cm.$^{-1}$. This band is independent of concentration up to 0·1M and weak hydrogen bonding comparable to that existing in 8-hydroxyquinoline is inferred. It may be noted that the low m. p. of *o*-benzylideneaminophenol compared with that for the *p*-isomer supports the view that intramolecular hydrogen bonding occurs in the former. *N*-Salicylideneaniline (VII), however, shows a diffuse band superimposed on the C–H stretching bands at *ca.* 2850 cm.$^{-1}$, and strong intramolecular hydrogen bonding involving a six-membered ring is inferred. With *o*-salicylideneaminophenol (VIII) the two hydroxyl absorption bands occur at 3550 and 3000 cm.$^{-1}$. Both hydroxy-groups are therefore bonded to the nitrogen atom. However comparison with the corresponding

TABLE 1. *Absorption of substituted 8-hydroxyquinolines in the hydroxyl stretching region.*

8-Hydroxyquinoline	M. p.	Ref.	ν_{OH}	$\Delta\nu$	$\Delta\nu_{\frac{1}{2}}$ [a]	A [a]
8-Hydroxyquinoline [b]	75°	—	3416	0	56	1·30
5-Fluoro-	110—110·5 [c]	*f*	3431	−15	56	1·38
5-Chloro-	125	*g*	3414	2	52	1·40
5-Iodo-	126—127	*h*	3387	29	— [d]	—
5-Formyl-	177—178 [e]	*i*	3358	58	64	2·09
5-Acetyl-	112	*j*	3357	59	64	2·18
5-Benzoyl-	117—118	*j*	3369	47	64	2·03
5-Methyl-	122—123	*g*	3413	3	57	1·55
5-Nitro-	173	*k*	3348	68	64	1·88
5-Phenylazo-	185—185·5	*l*	3391	25	64	2·48
5-Ethoxycarbonly-	125	*g*	3366	50	62	1·70
5 : 7-Dichloro-	179·5—180	*g*	3396	20	60	1·91
5 : 7-Dibromo-	197—198	*m*	3388	28	62	2·13
7-Chloro-	146	*g*	3396	20	59	1·53
5-Chloro-7-iodo-	177—178	*g*	3387	29	58	2·15
2-Methyl-	74	—	3408	8	61	1·57
5 : 7-Di-iodo-	210	*n*	3380	36	— [d]	—
5-Fluoro-7-iodo-	147—148 [e]	*o*	3404	12	— [d]	—

[a] In units of 10^4 moles^{-1} l. cm.$^{-2}$. [b] The hydroxyl stretching frequency reported here for 8-hydroxyquinoline (3416 cm.$^{-1}$) differs from that given by Flett (*Spectrochim. Acta*, 1957, **10**, 21) (3431 cm.$^{-1}$), but agrees reasonably with that reported by Mason (3412 cm.$^{-1}$). Our experience with the Grubb-Parsons S4 double-beam spectrometer is that it must be used without the wavelength cam, and calibrated by a method such as that of Downie, Magoon, Purcell, and Crawford (*J. Opt. Soc. Amer.*, 1954, **43**, 941) in order to justify an accuracy of ±1 cm.$^{-1}$. [c] Insufficient available for accurate determination. [d] Too insoluble for accurate determination. [e] Corrected. [f] Sample provided by Professor C. A. VanderWerf, *J. Org. Chem.*, 1952, **17**, 229. [g] Sample provided by Professor A. Albert. [h] Matsumura, *J. Amer. Chem. Soc.*, 1927, **49**, 810. [i] Clemo and Howe, *J.*, 1955, 3552. [j] Matsumura, *J. Amer. Chem. Soc.*, 1930, **52**, 4433. [k] Kostanecki, *Ber.*, 1891, **24**, 150. [l] Matsumura, *J. Amer. Chem. Soc.*, 1930, **52**, 4164. [m] Prepared by direct bromination. [n] Prepared by direct iodination. Helin and VanderWerf, *J. Org. Chem.*, 1952, **17**, 229.

TABLE 2. *Absorption of benzylideneaminophenols in the hydroxyl stretching region.*

Compound	M. p.	Ref.	ν_{OH}	$\Delta\nu_{\frac{1}{2}}$ [a]	A
p-Benzylideneaminophenol	183°	*a*	3618	—	—
o-Benzylideneaminophenol	89—90	*b*	3442	85	1·72
o-2-Nitrobenzylideneaminophenol	104	*a, c*	3459	70	1·56
o-3-Nitrobenzylideneaminophenol	131	*a, c*	3461	70	1·47
o-4-Nitrobenzylideneaminophenol	160—160·5	*a, c*	3458	66	1·49
o-4-Dimethylaminobenzylideneaminophenol	119	*c*	3420	108	2·06
o-4-Methoxybenzylideneaminophenol	91—91·5	*d*	3433	95	1·88
o-4-Chlorobenzylideneaminophenol	117—118	*e*	3448	79	1·77
o-4-Methylbenzylideneaminophenol	108—109	*f*	3434	88	1·76
N-Salicylideneaniline	51	*g*	*ca.* 2850	—	—
o-Salicylideneaminophenol	185	*d*	*ca.* 3550, *ca.* 3000		—

[a] Pope, *J.*, 1908, **93**, 532. [b] Pictet and Ankersmit, *Annalen*, 1891, **266**, 138. [c] Möhlau and Adam, *Chem. Zentr.*, 1907, I, 108. [d] Haegele, *Ber.*, 1892, **25**, 2753. [e] *o-4-Chlorobenzylideneaminophenol* was prepared from *o*-aminophenol and *p*-chlorobenzaldehyde in hot ethanol. It formed yellow needles, m. p. 117—118° (from ethanol) (Found: C, 67·3; H, 4·3. $C_{13}H_{10}ONCl$ requires C, 67·4; H, 4·4%). [f] Singleton and Pollard, *J. Amer. Chem. Soc.*, 1940, **62**, 2288. [g] Emmerich, *Annalen*, 1887, **241**, 341.

monohydroxy-compounds (OH absorptions at 3442 and 2850 cm.$^{-1}$, respectively) indicates that both bonds are weakened when the lone pair is shared in this way.

The effect of other substituents is best seen by the relation between the hydroxyl stretching frequency and Hammett's σ-values. The linear relation $\nu = \nu_0 + \rho_\nu\sigma$ has been fitted by the method of least squares with a standard deviation of ±2·2 cm.$^{-1}$. The value of ρ_ν (28·3) has the opposite sign to that found for phenols and catechols, *i.e.*, the effect of electron-attracting groups is to increase the hydroxyl frequency. This is consistent with the view that the substituents alter the electron density around the nitrogen atom but have little or no direct electronic effect on the hydroxyl group except through the hydrogen bond.

A linear relation ($A = A_0 + \rho_A\sigma$; $\rho_A = -0{\cdot}40$; standard deviation, 3·1% in A) also exists between the integrated intensities and the σ-constant, which contrasts with the phenols or 8-hydroxyquinolines in which no simple relation exists. This may be related mainly to the change in partial ionic character of the hydroxyl bond caused by hydrogen bonding which we have already suggested is determined by the electron density around the nitrogen atom. A similar relation ($\Delta\nu_{\frac{1}{2}}^{\sigma} = \Delta\nu_{0\frac{1}{2}}^{\sigma} + \rho\sigma$; $\rho = -27{\cdot}9$; standard deviation, ±2·6 cm.$^{-1}$) also exists for the half-intensity band-widths which are sensitive to changes in hydrogen bonding. On the other hand, the 8-hydroxyquinolines showed only minor variations and this may result from the opposing effect of electron-withdrawing substituents to decrease the electron density around the nitrogen but to increase the polarization of the hydroxyl bond.

FIG. 2. *Relation between the hydroxyl stretching frequency ν, and the σ-constant for the substituent. Rectangles indicate probable errors.*

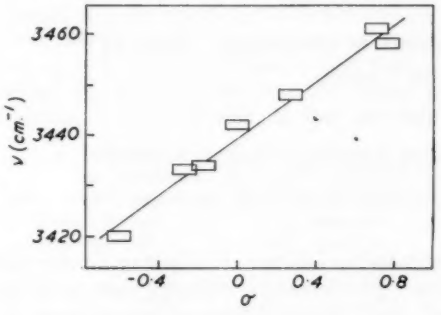
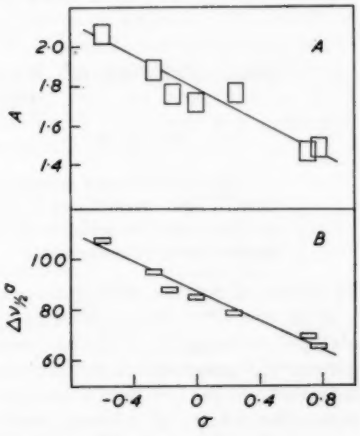


FIG. 3. *Relation between the integrated intensity A* (FIG. 3*A*) *and the half-intensity band width* $\Delta\nu_{\frac{1}{2}}^{\sigma}$ (FIG. 3*B*) *with the σ-constant of the substituent. Rectangles indicate probable errors* (±2 *cm.*$^{-1}$ *in* $\Delta\nu_{\frac{1}{2}}^{\sigma}$, 3% *in A*).



EXPERIMENTAL

Deuteration.—8-Hydroxyquinoline was dried in a vacuum over phosphoric oxide and then treated with a large excess of deuterium oxide (99·78%; d_4^{20} 1·10515; molar ratio > 100 : 1) at 80—90°. Under these conditions equilibrium was reached within a few seconds. The product was then dried in a vacuum and dissolved in freshly dried carbon tetrachloride. All operations were carried out in a dry-box to ensure the complete absence of water, as there was a rapid exchange with water vapour in solution. No C–D band could be detected in the product obtained in this way.

In another experiment a mixture of deuterium oxide and 8-hydroxyquinoline was made

slightly alkaline with solid potassium hydroxide and then heated at 80—90° for 36 hr. Sublimation at 80—90°/20 mm. gave the deuterated product, m. p. 74°, which showed C–D stretching vibration at *ca.* 2270 cm.$^{-1}$.

Infrared Spectra.—The spectra were determined with a Grubb-Parsons S4 double-beam spectrometer, a calcium fluoride prism being used. In the 3450—3340 cm.$^{-1}$ region ammonia gas was used for direct calibration before each determination. Reproducibility was better than ±1 cm.$^{-1}$ in this region where the effective slit width was *ca.* 8 cm.$^{-1}$. Dilute solutions (<0·005M) in carbon tetrachloride were examined in 2-cm. cells, intermolecular hydrogen bonding being unimportant at this concentration. The integrated absorption intensities were measured by a method similar to that of Brown and Rogers [14] except that the limits of integration were extended to ±140 cm.$^{-1}$ (±180 cm.$^{-1}$ for the benzylideneaminophenols). The absolute accuracy is difficult to evaluate but a re-determination of *n*-propyl alcohol gave $A = 0{\cdot}52$, in good agreement with the literature value.[14] The relative intensities are considered to be within 3—5%.

We thank Professors Adrien Albert and C. A. VanderWerf for generous gifts of 8-hydroxyquinoline derivatives, and the Rockefeller Foundation for a grant for the purchase of the infrared spectrometer. One of us (A. G. M.) has been working with a C.S.I.R.O. Scholarship.

UNIVERSITY OF ADELAIDE, SOUTH AUSTRALIA. [*Received, March 31st,* 1958.]

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694. *Addition of Methyl Radicals to Quinones. Part II.* The Reaction Centre.*

By R. P. BUCKLEY, A. REMBAUM, and M. SZWARC.

The relative rate constants of addition of methyl radicals to substituted benzo- and naphtha-quinones were determined. They are considered as evidence for the addition of methyl radicals to the C=C and not to the C=O double bond of quinones.

REACTION of radicals with quinones is undoubtedly by addition, which may involve the C=O or the C=C double bond of the quinone. The literature indicates that both are attacked, although by different types of radical: the C=O double bond of benzoquinone by polystyryl,[1] poly(methyl methacrylate),[2a] poly(methyl acrylate),[2b] and 2-cyano-2-propyl radicals,[3] and the C=C double bond of naphthaquinone by methyl.[4,5] In all these investigations the centres of addition were identified by examining the products. The shortcomings of such a method have been discussed [6] and an alternative method based on kinetic evidence was outlined. The results reported indicated that methyl radicals add to the C=C double bonds of quinones, confirming Fieser and Oxford's findings.[4] We now report new results which confirm this conclusion, though we emphasize that our results are pertinent only to the methyl radicals.

As in our earlier work,[6,7] results are given as the ratio k_2/k_1; the subscripts refer to the hydrogen abstraction reaction (1):

$$CH_3 + \text{Solvent} \longrightarrow CH_4 + \text{Solvent radical} \quad \ldots\ldots\ldots (1)$$

and to the addition reaction (2)

$$CH_3 + Q \longrightarrow Q{\cdot}CH_3 \quad \ldots\ldots\ldots (2)$$

where Q denotes a molecule of a quinone.

* Part I, *J. Amer. Chem. Soc.*, 1955, **77**, 4468.

[1] Cohen, *J. Amer. Chem. Soc.*, 1947, **69**, 1057.
[2] Kice, (*a*) *ibid.*, 1954, **76**, 6274; (*b*) *J. Polymer. Sci.*, 1956, **19**, 123.
[3] Bickel and Waters, *J.*, 1950, 1746; Aparicio and Waters, *J.*, 1952, 4666.
[4] Fieser and Oxford, *J. Amer. Chem. Soc.*, 1942, **64**, 2060.
[5] Kvalnes, *ibid.*, 1934, **56**, 2478.
[6] Rembaum and Szwarc, *ibid.*, 1955, **77**, 4468.
[7] Levy and Szwarc, *ibid.*, p. 1949 and subsequent papers.

We have shown [6,8] that a carbon atom to which a methyl radical might be added can be " blocked " by substituting methyl groups or chlorine atoms for hydrogen atoms. Apart from the " blocking " effect a methyl group only slightly affects the reactivity. On the other hand, a chlorine atom powerfully activates the C=C double bond, although a completely chlorinated double bond is unreactive owing to the " blocking " effect of the chlorine atoms. These observations were considered in the previous paper [6] as crucial in deciding which centre was attacked by methyl radicals. It was pointed out that the decrease in the reactivity (*i.e.*, in k_2/k_1) along the series benzoquinone, toluquinone, 2 : 5-xyloquinone, and duroquinone reflects the " blocking " effect of methyl groups. Supporting evidence was provided by the series, naphthaquinone, 2-methylnaphthaquinone and 2 : 3-dimethylnaphthaquinone, where the value of k_2/k_1 also decreases. On the other hand, the reactivity of 2 : 7-dimethyl- differs little from that of 2-methyl-naphthaquinone, showing that a methyl group substituted away from the relevant C=C double bond has negligible effect on the reactivity.

It may be argued, however, that the methyl groups sterically hinder the addition to the C=O bonds. Indeed, the methyl groups in the substituted benzoquinones and the corresponding naphthaquinones are adjacent to the C=O bonds, and they might therefore interfere with the addition to this centre. If so, reactivities of methylated quinones do not allow us to differentiate between the two alternative modes of addition. It should be stressed that the results in Table 1 clearly show 2 : 3-, 2 : 5-, and 2 : 6-dimethylquinones to be equally reactive in respect to methyl-radical addition. Furthermore, their reactivities (*i.e.*, k_2/k_1's) are approximately half that of unsubstituted benzoquinone ($k_2/k_1 = 2020$, see ref. 6), indicating that the two methyl groups " blocked " two of the four centres of addition.

TABLE 1. *Reaction of quinones in toluene at* 65° ($Ac_2O_2 = \sim 0{\cdot}02$M).

Mole (%)	k_2/k_1	Mole (%)	k_2/k_1	Mole (%)	k_2/k_1	Mole (%)	k_2/k_1
2 : 5-Dimethyl-benzoquinone		2 : 6-Dimethyl-benzoquinone		2 : 3-Dimethyl-benzoquinone		2 : 5-Dichloro-benzoquinone	
0·1	1100	0·1	1100	0·1	910	0·02	5130
0·1	910	0·1	1200	0·1	1150	0·03	4860
0·1	970	0·1	1300	Average 1030 ± 85		0·04	5560
0·1	990	0·1	1150			0·05	5340
0·5	1160	Average 1190 ± 80				Average 5220 ± 300 †	
Average 1030 ± 90 *							
2 : 3-Dichloro-benzoquinone		2-Chloro-1 : 4-naphthaquinone		6 : 7-Dichloro-1 : 4-naphthaquinone		2 : 6-Dimethoxy-benzoquinone	
0·02	1460	0·041	2390	0·039	880	0·032	317
0·04	1270	0·061	2240	0·098	1010	0·046	386
0·09	1500	0·102	1870	0·157	1030	0·064	299
0·10	1520	0·163	2180	Average 970 ± 80		0·096	360
0·10	1690	Average 2170 ± 220				Average 340 ± 40	
0·10	1330						
0·10	1110						
0·16	1490						
0·17	1600						
Average 1330 ± 300							

Averages reported in Part I are * 870, † 5240.

On the other hand, by investigating the reactivities of chlorinated quinones the two modes of addition can be distinguished. Earlier in this paper it was noted that a chlorine atom substituted at a double bond has a strongly activating effect although dichlorination of such a bond results in complete " blocking " and consequent decrease in reactivity.

The reactivity of monochlorobenzoquinone was 3450 (ref. 6), compared with 2020 for benzoquinone itself. If it is assumed that one of the C=C double bonds of the chloroquinone remains as reactive as a C=C double bond of the unsubstituted quinone, the effect of a

[8] Szwarc and his co-workers, *J. Amer. Chem. Soc.*, p. 5493; 1956, **78**, 5696; 1957, **79**, 5621, 6343.

chlorine atom on the reactivity of the other C=C bond is given by a factor of 2·4. In 2 : 5- and 2 : 6-dichlorobenzoquinone both double bonds are activated by chlorine atoms and k_2/k_1 values were 5240 and 5130 (see ref. 6). The value of k_2/k_1 for 2 : 5-dichlorobenzoquinone was redetermined in the present work and found to be 5220 (see Table 1), in

TABLE 2. *Reactivity of naphthaquinone in toluene at* 65°.

Mole % of quinone	CH_4	CO_2	CH_4/CO_2	k_2/k_1	Mole % of quinone	CH_4	CO_2	CH_4/CO_2	k_2/k_1
Series A					*Series B*				
—	0·458	0·683	0·669	—	—	0·392	0·598	0·656	—
0·052	0·575	1·050	0·546	433	—	0·432	0·617	0·700	—
0·130	0·320	1·150	0·278	1082	0·051	0·501	1·110	0·451	986
0·156	0·287	0·806	0·324	683	0·127	0·310	1·130	0·274	1161
0·208	0·211	0·855	0·247	821	0·153	0·275	1·120	0·246	1148
					0·204	0·212	1·100	0·193	1232
Series C									
—	0·406	0·591	0·687	—					
—	0·402	0·601	0·669	—					
0·051	0·362	0·803	0·451	986					
0·128	0·200	0·676	0·296	1009					
0·154	0·184	0·688	0·267	999					
0·205	0·139	0·670	0·207	1110					
			Average 1080 ± 100						

Series *A*: recryst. from ligroin.
Series *B*: recryst. from ligroin, then from EtOH; m. p. 124°.
Series *C*: recryst. from EtOH, then sublimed *in vacuo*; m. p. 124—125°.

Apparently series A was carried out with insufficiently pure compound. The results of series B and C were reproducible and self-consistent in CH_4/CO_2 ratio and therefore in k_2/k_1. However, it seems that the compound used in the series B contained some impurities which induced the decomposition of the peroxide, increasing the amounts of CH_4 and of CO_2 formed, although apparently they did not affect the ratio CH_4/CO_2; this impurity seems to be largely removed in series C.

agreement with the previous value. On this basis the effects of chlorine atoms in these compounds can be calculated to be 2·6 and 2·5 per double bond respectively, in agreement with the other value.

The reactivity of 1 : 4-naphthaquinone was redetermined in the present work. The relevant data (Table 2) show that the extent of purification of the compound appears to be critical. On the basis of the values obtained in series *B* and *C*, the k_2/k_1 for 1 : 4-naphthaquinone is 1080 ± 90, *i.e.*, the same as k_2/k_1 per double bond of benzoquinone or 2 : 3-dimethylbenzoquinone. The same value (970 ± 80) was obtained for 6 : 7-dichloronaphthaquinone (see Table 1), indicating that chlorine atoms remote from the centre of reaction affect its reactivity very slightly. The k_2/k_1 for 2-chloro-1 : 4-naphthaquinone was found to be 2170 ± 220; thus, the effect of a chlorine atom on the reactivity of the particular C=C double bond amounts to a factor of 2·0.

In contrast to all these observations k_2/k_1 for 2 : 3-dichlorobenzoquinone was found to be 1330 ± 300 (*i.e.*, a value corresponding to one C=C double bond only). Hence, this result shows convincingly that the addition of methyl radicals to quinones takes place on a C=C double bond and not on a C=O double bond. If the latter bond were involved in the reaction then a low value would be observed for 2 : 6-dichlorobenzoquinone, which contradicts the actual observations. Apparently the two chlorine atoms in 2 : 3-dichlorobenzoquinone " block " one of the C=C double bonds and have a negligible effect on the reactivity of the other C=C bond. In this respect 2 : 3-dichlorobenzoquinone behaves like 6 : 7-dichloronaphthaquinone.

Finally, the reactivity of 2 : 6-dimethoxybenzoquinone deserves comment. The methoxy-group deactivates the C=O double bond for methyl-radical addition. Accepting the previous approach it is concluded that a methoxy-group deactivates a C=C double bond of benzoquinone by a factor of 0·17. A similar result can be obtained from the reactivity of 2-methoxybenzoquinone (k_2/k_1 1060). Assuming that only one C=C bond in this compound was deactivated affords a value of 0·05. Here the deactivating effect of the

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methoxy-group can only be given as an order of magnitude since it was obtained as a small difference between two large numbers.

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DEPT. OF CHEMISTRY, STATE UNIVERSITY COLLEGE OF FORESTRY, SYRACUSE UNIVERSITY, SYRACUSE 10, N.Y., U.S.A. [*Received, April 9th*, 1958.]

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695. *The Kinetics of Catalytic Polymerisations. Part XI.* Polymerisation of α-Methylstyrene catalysed by the Chloroacetic Acids.*

By C. P. BROWN and A. R. MATHIESON.

Kinetics of the ionic polymerisation of α-methylstyrene catalysed by mono-, di-, and tri-chloroacetic acids have been investigated. The dependence of the initial rates on initial monomer ($[M]_0$) and catalyst ($[C]_0$) concentrations is $-d[M]_0/dt = k_0[M]_0^2[C]_0^{3\cdot2}$ and $-d[C]_0/dt = k_0'[C]_0$ for reactions in the absence of solvent, $-d[M]_0/dt = k_0[M]_0^2[C]_0^2$ and $-d[C]_0/dt = k_0'[M]_0^2[C]_0^2$ for ethylene dichloride solutions, and $-d[M]_0/dt = k_0[M]_0^2[C]_0$ for nitromethane solutions. After the initial stage in absence of solvent the kinetic order changes and becomes unity with respect to [M]. The acid catalysts are rapidly consumed initially, then more slowly, and finally may be regenerated. The rates of polymerisation are between 6 and 1960 times greater than for styrene and the effectiveness of the catalysts is related to their acid strengths. Reaction rate and overall activation energy increase with the dielectric constant of the medium, but the polymer molecular weight is only slightly changed. Polymers formed at room temperature are of low molecular weight, chiefly dimer and trimer; some of these are unsaturated, and the remainder and the higher polymer carry terminal chloroacetate groups, as shown by chemical and infrared analysis. The molecular weight increases at high values of $[C]_0$ and lower reaction temperatures; its distribution does not change during the reaction.

THE kinetics and mechanism of the polymerisation of styrene catalysed by the chloroacetic acids have already been studied;[1,2,3] the results of a similar study of α-methylstyrene are reported here. In general, as with catalysis by chloroacetic acids,[4] α-methylstyrene is cationically polymerised more rapidly than styrene, but forms polymers of only very low molecular weight at room temperature.[5] A detailed comparison of the two monomers in these systems should help to elucidate the special behaviour of α-methylstyrene towards polymerisation. As for styrene, the reaction rates are very sensitive to reactant concentrations and high acid concentrations must be employed to obtain measurable rates.

Recent studies of the polymerisation of α-methylstyrene by metal halide catalysts[6,7,8] have shown that the rate is proportional to $[M]^x[C]$, where x can have values from 1 to 2 depending on reaction conditions. The polymers may be largely unsaturated,[8] or saturated,[7] and have substituted phenylindane end groups.[6] The polymer molecular weights are proportional to $[M]$.[6,8] α-Methylstyrene will not polymerise[9,10] ionically

* Part X, *J.*, 1957, 3631.

[1] Brown and Mathieson, *J.*, 1957, 3612.
[2] Brown and Mathieson, *J.*, 1957, 3620.
[3] Brown and Mathieson, *J.*, 1957, 3631.
[4] Pepper, *Quart. Rev.*, 1954, **8**, 88.
[5] Brown and Mathieson, *J.*, 1957, 3608.
[6] Dainton and Tomlinson, *J.*, 1953, 151.
[7] Jordan and Mathieson, *J.*, 1952, 2354.
[8] Worsfold and Bywater, *J. Amer. Chem. Soc.*, 1957, **79**, 4917.
[9] Dainton and Ivin, *Nature*, 1948, **162**, 705; *Trans. Faraday Soc.*, 1950, **46**, 331.
[10] McCormick, *J. Polymer Sci.*, 1957, **25**, 488.

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above 61° and has a low heat of polymerisation.[10,11] This led Dainton and Ivin [9] to suggest that depropagation was important but Worsfold and Bywater [8] concluded that it is not significant for the formation of short chains. Steric hindrance to polymerisation has been suggested [12] to explain low molecular weights and heat of polymerisation, but very high polymers can be made at low temperatures.[13] Decreased importance of transfer relative to termination at low temperatures has been suggested to explain this.[14]

Results and Discussion

General Features of the Reactions.—The polymerisations, studied in ethyl bromide, ethylene dichloride, and nitromethane, and in the absence of solvent, are quantitative. At room temperature the main products (a sticky solid or viscous liquid) are dimer and trimer, even in nitromethane, but at higher catalyst concentrations some polymer of molecular weight 1000—1500, precipitated by methanol, is formed along with the methanol-soluble dimer–pentamer. The reaction rates are appreciably faster than for styrene and yellow-brown colours in the product are developed more rapidly, but are easily destroyed by washing with water to remove excess of acid. The reactions, more rapid in media of high dielectric constant, do not proceed in nitrobenzene, acetone, or alcohol, and are retarded by *p*-benzoquinone and 1 : 3 : 5-trinitrobenzene, presumably by the same mechanism as that established for styrene [1] since the same red colour appears and quinhydrone is precipitated. Monochloroacetic acid is an effective catalyst, in contrast to its inertness towards styrene, but acetic acid has no effect even in nitromethane. The rate of reaction is greater the greater the acid strength of the catalyst, but the molecular weight and composition of the product are similar for the three acids. The acid is rapidly consumed at first, the rate decreasing as reaction proceeds as for styrene, but the acid can be re-formed towards the end.

The methods used to follow the rates of consumption of monomer and acid need careful consideration before they can be related to the true rates of reaction. Measurements of acid concentration were based on extraction of residual free acid into water. Those of monomer concentration were based on direct bromination in the polymerising solution, so monomer and acid would not appear to be consumed by reversible formation of a monomer–acid complex. Also, a considerable fraction of the polymer formed at room temperature consists of unsaturated dimer and trimer which readily take up bromine, so it was necessary to separate the product quantitatively and measure its bromine uptake for each determination of monomer consumption during the reaction. The amount of product separated also checked the bromine titration method.

Molecular Weight and Composition of the Product.—A series of reactions was carried out with di- and tri-chloroacetic acids in which the product was quantitatively separated and its molecular weight ($\overline{M}_n$) measured (Table 1). The average molecular weight is only slightly greater for reactions in nitromethane than in the absence of solvent but at high catalyst concentrations it increases with catalyst concentration, more pronouncedly than for styrene. This can be represented approximately as

$$\overline{M}_n = 236 + 6[\mathrm{C}]_0^2$$

The effect of temperature on molecular weight was studied by using only ethyl bromide as solvent, since at −80° the rate in non-polar solvents such as *iso*pentane was too small to measure. The molecular weight is higher for reactions at low temperatures, and, as for the styrene–chloroacetic acid [1] and α-methylstyrene–aluminium chloride [14] systems, $\log (1/\overline{M}_n) \propto 1/T(°\mathrm{K})$. At −80° the poly-α-methylstyrene formed has approximately

[11] Roberts and Jessup, *J. Res. Nat. Bur. Stand.*, 1951, **46**, 11.
[12] Evans and Polanyi, *Nature*, 1948, **152**, 738.
[13] Hersberger, Reid, and Heiligmann, *Ind. Eng. Chem.*, 1945, **37**, 1073.
[14] Jordan and Mathieson, *J.*, 1952, 2363.

the same molecular weight as polystyrene formed under the same conditions. Evidently the factors which limit molecular weight and produce large amounts of dimer at room temperature are not important at low temperatures.

TABLE 1. *Molecular weight of the polymer.*

A. *Effect of acid concentration* ($[C]_0$). (Dichloroacetic acid in nitromethane, 25°.)

$[C]_0$ (mole l.$^{-1}$), $\overline{M}_n$	3·1, 265	4·6, 330	6·3, 430	7·6, 550

B. *Effect of temperature.* (Trichloroacetic acid in ethyl bromide.)

Temp., $\overline{M}_n$	−80°, 2400	0°, 400	40°, 250

C. *Effect of extent of reaction.* (Trichloroacetic acid, no solvent, $[C]_0$ = 1·0 mole l.$^{-1}$, 25°.)

Monomer conversion (%)	18·3	29·6	54·3	71·8	89·9
$\overline{M}_n$	380	370	370	385	365

D. *Limiting viscosity number* ($[\eta]$). (In benzene, 25°.)

$[\eta]$	0·0080	0·012	0·017	0·0185	0·0190	0·0235	0·0245	0·0275
$\overline{M}_n$	270	330	460	500	560	600	690	770

E. *Effect of solvent.* (Dichloroacetic acid, $[C]_0$ = 1·0 mole l.$^{-1}$, 25°.)

Solvent, $\overline{M}_n$	None, 370	Nitromethane, 400

The limiting viscosity number–number-average molecular weight relationship is $[\eta] = 3{\cdot}50 \times 10^{-5}\overline{M}_n$ for unfractionated polymers prepared at normal temperatures, with concentration expressed as grams of polymer per 100 ml. of solution at 25°. These values of $[\eta]$ are somewhat greater that those for poly-α-methylstyrenes of comparable molecular weight prepared by other methods, perhaps owing to the chloroacetate end-groups.

TABLE 2. *Molecular-weight distribution.*

A. *At end of reaction.* (Trichloroacetic acid, 25°.) Weight % of polymer in various fractions given.

System:	(*a*) No solvent $[C]_0$ = 1·0			(*b*) $CH_3{\cdot}NO_2$ soln. $[C]_0$ = 1·0			(*c*) $CH_3{\cdot}NO_2$ soln. $[C]_0$ = 5·0		
Range of M_n	(1)	(2)	(3)	(1)	(2)	(3)	(1)	(2)	(3)
236—350	55·8	59·3	61·7	46·3	47·2	51·6	42·8	45·7	50·1
350—500	27·2	26·9	21·8	23·8	20·9	21·3	18·7	19·6	15·3
500—800	13·6	13·9	14·3	28·3	28·7	21·6	21·7	16·5	19·8
>800	0	0	0	0	0	0	17·3	16·1	15·6

B. *Effect of extent of reaction.* (Dichloroacetic acid, no solvent, $[C]_0$ = 1·0, 25°.)

Monomer conversion (%)	38·5	48·3	59·6	61·7	75·1	100
Fraction $\overline{M}_n$ = 236—350 as weight % of polymer	55·0	57·5	54·7	53·5	51·0	58·3

The molecular-weight distribution was measured for three systems at 25° with trichloroacetic acid, (*a*), (*b*), and (*c*) (Table 2). Three polymers were fractionated for each system. The highest fraction, which appeared only when the catalyst was in high concentration, was insoluble in methanol and had a molecular weight between 1000 and 1500. Reproducibility in the fractionation was reasonably good for the low-pressure distillation method used. There was no change in the molecular-weight distribution with extent of reaction.

Constitution and Stability of Polymers.—Polymers were microanalysed for carbon, hydrogen, and chlorine and examined for unsaturation by catalytic microhydrogenation (Table 3). Nos. 1, 2, and 3 are further fractions obtained by fractionating the 236—350 fraction. They have one double bond per molecule and no chloroacetate group. The fraction 236—350 is clearly a mixture of unsaturated dimer (236) and unsaturated trimer (354). Nos. 5 and 6 are the 350—500 fraction. They are fully saturated and contain one trichloroacetate group per molecule and are evidently dimer trichloroacetate (398) and some trimer trichloroacetate (516). Nos. 9—12 are unfractionated polymers of low molecular weight, showing how the proportion of unsaturated molecules falls as molecular weight rises. Nos. 7 and 8 are the >800 fraction and are fully saturated but contain less than one chloroacetate group per polymer molecule. Distillation of the esterified polymers

at atmospheric pressure expels the chloroacetate group leaving a terminal double bond, as for polystyrene, and No. 4 is the 500—800 fraction which has been distilled.

Poly-α-methylstyrene prepared by chloroacetic acid catalysis consists of unsaturated

TABLE 3. *Microanalysis of the polymers.*

No.	(M_n)		C (%)	H (%)	Cl (%)	No. of double bonds per molecule	No. of trichloroacetate groups per molecule
1	240	Fraction 236—500	91·1	8·6	0	0·97	0
2	245	,,	90·1	8·4	0·4	1·0	0·010
3	354	,,	89·2	8·2	0·9	1·0	0·031
4	472	Fraction 500—800, distilled	89·9	7·9	0	1·0	0
5	423	Fraction 350—500	59·5	5·2	24·6	0	0·98
6	450	,,	59·2	5·5	24·3	0	1·02
7	1200	Fraction >800	85·0	6·9	2·1	0	0·24
8	1560	,,	85·1	7·0	3·8	0	0·54
9	260	Unfractionated	—	—	—	1·13	—
10	280	,,	—	—	—	1·01	—
11	320	,,	—	—	—	0·67	—
12	360	,,	—	—	—	0·18	—

dimer and trimer, dimer and trimer esters and higher esters, and perhaps some higher-molecular weight material which contains neither double bonds nor chloroacetate groups. From the molecular-weight distributions, the analyses of the polymers, and the average

TABLE 4. *Approximate composition (weight %) of polymers formed at 25°.*

System	No solvent	$CH_3{\cdot}NO_2$ solution	$CH_3{\cdot}NO_2$ solution $[C]_0 = 5{\cdot}0$
Unsaturated dimer	47	37	37
Unsaturated trimer	12	9	9
Dimer ester	25	22	18
Trimer—pentamer ester	14	26	19
Higher polymer	0	0	16

molecular weights of the fractions, the composition of the polymers is approximately as shown in Table 4. The composition is not significantly altered by change of acid, or by the use of ethylene dichloride as solvent, but nitromethane increases the proportion of higher esters, and high initial catalyst concentrations lead to the formation of some higher polymer.

The interpretation of chlorine content in terms of chloroacetate groups receives confirmation from the infrared spectra of the polymers (Table 5). Sample II was prepared by trichloroacetic acid catalysis in the absence of solvent. Sample III is a portion of sample II hydrolysed by refluxing it with potassium hydroxide in octyl alcohol to remove trichloroacetate groups. Sample I is thermal polystyrene for comparison. The spectrum of ethyl trichloroacetate was measured for comparison (Table 6), and comparison can also be made with the spectra of polystyrene prepared by trichloroacetic acid catalysis and of benzyl trichloroacetate.[2] The bands at 815 m, 1245 s, 1290 m, and 1760 s in sample II indicate that it contains combined trichloroacetate residues and these are reduced to 806 w, 1245 m, 1290 w, and 1760 w in the hydrolysed sample III. Bands at 720 and 1090 (sample II and III) could be due to *ortho*-disubstitution, and the 2870 band in sample I occurs in sample II but is absent from sample III. It could be due to ≡CH converted by the removal of a combined chloroacetate group into $>CH_2$. This suggests the occurrence of the substituted indane structure. The presence of a small amount of free trichloroacetic acid in sample II may be indicated by the band at 2520 m. Bands at 1795 and 3040 in samples II and III are due to $-CH{=}CH_2$ groups in the unsaturated dimer and trimer, and that at 1390 is due to the methyl groups.

Initial Rates of Polymerisation.—The rates of monomer consumption were measured

at 25° with all three acids in the absence of solvent, and in ethylene dichloride and nitromethane solutions. Fig. 1 shows typical reaction–time curves, which were reproduced to about 2%. The sealed-tube method was used. The results are collected in Table 7, which shows the linear dependence of the initial rates on the appropriate powers of $[M]_0$ and $[C]_0$. The water concentration was within the range for which the rate was independent

TABLE 5. *Infrared spectra of the polymers* (*cm.*$^{-1}$) (s, *absorption* > 70%; m, 30—70%; w < 30%).

Sample No.	I	II	III	I	II	III	I	II	III
	667m	—	—	1077m	1077m	1083m	—	1580m	1580m
	683s	683s	680s	—	1090w	1100m	1585m	1585s	1585s
	700s	690s	700s	1150m	1150m	1150m	1610s	1610w	—
	—	720m	720w	1175m	—	—	1680w	1670w	1670w
	760s	760s	760s	1185m	1185m	1180m	1730m	—	—
	—	780m	780m	1215w	—	—	—	1760s	1760w
	—	815m	806w	—	1245m	1245m	—	1795m	1795m
	850m	853m	840w	1285m	1290m	1290w	1810m	1825m	1830m
	—	890m	—	1295m	—	—	1860m	1875m	1880m
	910s	910m	900m	—	1315w	1315w	1930m	1905m	—
	930m	930m	—	1350m	1365m	1370m	—	2520m	—
	950m	965m	950m	—	1390m	1390m	2870m	2870m	—
	985m	—	—	1450m	1450m	1450m	2950s	2980s	2950m
	993m	1000m	1000w	1470m	1470m	1470m	—	3040s	3040m
	1015m	1015s	1030s	1485s	—	—	—	3140m	3140m
	1045m	1050m	—	—	1505s	1505s	3190m	3190m	3190m
	—	1057s	—	1545w	1550s	1550s	3220m	—	—

TABLE 6. *Infrared spectrum of ethyl trichloroacetate* (*cm.*$^{-1}$).

683w *	750w	828s *	960s	1100m *	1160s *	1229m *	1266m	
1300s *	1370m	1393m	1445m	1470m	1760m *	2976m	—	

* Characteristic of trichloroacetate group.)

of water concentration for styrene. From the similarity of this polymerisation to that of styrene it is presumed that the rate in the absence of solvent depends on water concentration at low water concentrations, but this has not been experimentally demonstrated for α-methylstyrene. The kinetic orders are the same for all three acids in a given medium, and the initial rates are described by the equations

$$-d[M]_0/dt = k_0[M]_0^2[C]_0 \text{ for nitromethane solutions}$$

$$-d[M]_0/dt = k_0[M]_0^2[C]_0^2 \text{ for ethylene dichloride solutions}$$

$$-d[M]_0/dt = k_0[M]_0^2[C]_0^{3\cdot2} \text{ in absence of solvent}$$

These kinetic orders are the same as for styrene,[1] except that 3·2 replaces 3·5 as exponent of $[C]_0$ in the last. The initial rates given in Table 7 were obtained from experiments in

TABLE 7. *Initial rates of polymerisation* (*mole l.*$^{-1}$ *min.*$^{-1}$) *at* 25°.

Medium	No solvent		Ethylene dichloride		Nitromethane.	
Acid	Initial rate	$[M]_0^2[C]_0^3$	Initial rate	$[M]_0^2[C]_0^2$	Initial rate	$[M]_0^2[C]_0$
$CH_2Cl\cdot CO_2H$	3·28 × 10^{-6}	210	3·43 × 10^{-5}	0·35	0·48 × 10^{-4}	3·6
	4·12 ,,	264	5·22 ,,	0·54	1·10 ,,	8·5
	4·75 ,,	303	7·28 ,,	0·75	1·65 ,,	12·1
	5·52 ,,	354	8·83 ,,	0·92	2·09 ,,	16·0
	6·80 ,,	430	11·1 ,,	1·13	2·52 ,,	19·4
$CHCl_2\cdot CO_2H$	3·0 × 10^{-3}	226	2·68 × 10^{-5}	0·24	0·042	3·2
	4·1 ,,	294	4·78 ,,	0·44	0·106	8·2
	4·7 ,,	340	6·22 ,,	0·58	0·152	11·8
	5·7 ,,	400	8·32 ,,	0·78	0·198	15·5
	6·8 ,,	475	11·6 ,,	1·06	0·258	20·2
$CCl_3\cdot CO_2H$ ...	2·43 × 10^{-2}	194	2·85 × 10^{-4}	0·26	0·28	2·6
	3·24 ,,	251	4·47 ,,	0·41	0·78	7·1
	4·05 ,,	311	6·75 ,,	0·60	1·22	11·3
	4·73 ,,	363	9·18 ,,	0·82	1·63	15·0
	6·23 ,,	454	12·2 ,,	0·99	2·04	18·8

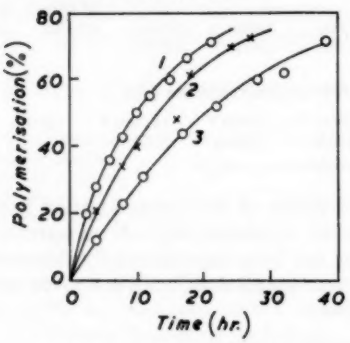
which both $[M]_0$ and $[C]_0$ were varied. In addition, the exponent 3·2 was checked for di- and tri-chloroacetic acid catalysis by experiments with constant $[M]_0$, and $[C]_0$ varied by using

TABLE 8. *Overall initial rate constants at 25° (mole l.$^{-1}$ min.$^{-1}$).*

System	k_0 (α-methylstyrene)	k_0 (styrene)
$CCl_3 \cdot CO_2H$–no solvent	$1{\cdot}30 \times 10^{-3}$	$3{\cdot}1 \times 10^{-6}$
$CHCl_2 \cdot CO_2H$–no solvent	$1{\cdot}43 \times 10^{-4}$	$7{\cdot}3 \times 10^{-8}$
$CH_2Cl \cdot CO_2H$–no solvent	$1{\cdot}56 \times 10^{-7}$	0
$CCl_3 \cdot CO_2H$–$C_2H_4Cl_2$	$1{\cdot}13 \times 10^{-3}$	$1{\cdot}85 \times 10^{-3}$
$CHCl_2 \cdot CO_2H$–$C_2H_4Cl_2$	$1{\cdot}08 \times 10^{-3}$	$3{\cdot}12 \times 10^{-5}$
$CH_2Cl \cdot CO_2H$–$C_2H_4Cl_2$	$9{\cdot}7 \times 10^{-7}$	0
$CCl_3 \cdot CO_2H$–$CH_3 \cdot NO_2$	0·110	$7{\cdot}3 \times 10^{-3}$
$CHCl_2 \cdot CO_2H$–$CH_3 \cdot NO_2$	$1{\cdot}28 \times 10^{-3}$	$1{\cdot}6 \times 10^{-4}$
$CH_2Cl \cdot CO_2H$–$CH_3 \cdot NO_2$	$1{\cdot}30 \times 10^{-5}$	0

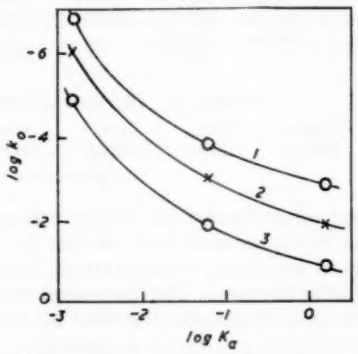
ethylene dichloride and ethyl chloride as diluents for the two acids respectively so as not to alter the dielectric constant of the system. Plots of log $(-d[M]_0/dt)$ against log $[C]_0$ gave straight lines of slope 3·2. The values of the overall initial rate constants (k_0) are

FIG. 1. *Typical reaction–time curves for trichloroacetic acid catalysis in nitromethane solution* (25°).



1, $[C]_0 = 0{\cdot}50$; 2, $[C]_0 = 0{\cdot}37$; 3, $[C]_0 = 0{\cdot}25$.

FIG. 2. *Catalytic activity and acid strength* (25°).



1, No solvent; 2, ethylene dichloride solution; 3, nitromethane solution.

shown in Table 8, together with the corresponding values for styrene.[1] (The units of k^0 for styrene, not specified in ref. 1, are mole l.$^{-1}$ min.$^{-1}$.) Although α-methylstyrene is more rapidly polymerised than styrene in every case, the relative rate is different in each system, lying between 6·1 for trichloroacetic acid–ethylene dichloride and 1960 for the dichloro-acid with no solvent. For a particular solvent, the relative rate for dichloroacetic acid catalysis is always greater than for trichloroacetic acid catalysis and the ratio of the value of the function $[k_0$ (α-methylstyrene)$/k_0$(styrene)] with dichloroacetic to that with trichloroacetic acid is roughly constant, being 4·7, 5·7, and 5·3 for no solvent, ethylene dichloride solution, and nitromethane solution, respectively. The relative rate for a particular acid does not depend on the dielectric constant of the medium, being in the order no solvent $\gg$ nitromethane solutions $>$ ethylene dichloride solutions.

Comparison of the Catalytic Activities of the Chloroacetic Acids.—The catalysts are more effective the greater their acid strengths, but the overall initial rate constants do not obey the relation $k_0 = GK_a^x$, where K_a is the acid dissociation constant and G and x are constants for a given reaction. Fig. 2 shows plots of log K_a against log k_0 for the three media, and the three curves are similar. The rate of an ionic polymerisation depends on other factors than the proton-donating power of the catalyst, but nevertheless k_0 and K_a

are related although the Brønsted relation cannot be expected to hold. If the polymerisation proceeds by a mechanism similar to that postulated for styrene,[3] as the kinetic orders suggest, it may be that the acid strength of the catalyst influences the reactivity of the monomer–catalyst complex in initiation and propagation.

Influence of Dielectric Constant and Temperature on the Polymerisation.—The rate is greater in media of higher dielectric constant (Tables 7 and 8), as for styrene,[1] and demonstrates the ionic character of the polymerisation. The overall initial rates of polymerisation were determined at 0°, 25°, and 40° for the three media. The Arrhenius

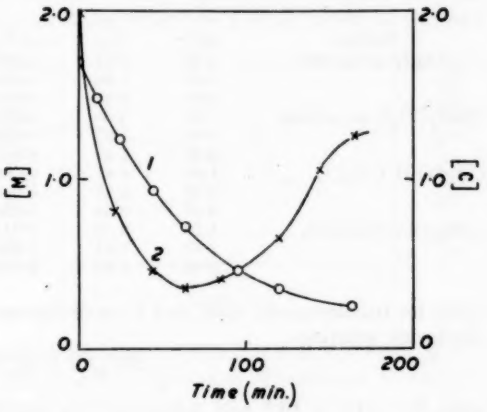


FIG. 3. *Consumption of monomer and acid during reaction for dichloroacetic acid catalysis in ethylene dichloride solution (25°).*

1, Monomer; 2, acid.

equation is obeyed over this range of temperature and the overall energies of activation (E_0) are shown in Table 9. The value of E_0 increases with dielectric constant of the sol-

TABLE 9. *Overall energy of activation* (E_0) (*kcal. mole*$^{-1}$).

Medium	Dielectric constant	$CCl_3 \cdot CO_2H$	$CHCl_2 \cdot CO_2H$	$CH_2Cl \cdot CO_2H$
No solvent	—	14	6·5	4·0
$C_2H_4Cl_2$	10·5	8	6·0	6·5
$CH_3 \cdot NO_2$	39	15	—	8·0

vent, though the reactions in absence of solvent seem anomalous. The values for trichloroacetic acid are greater than for di- and mono-chloroacetic acid. In general, as for styrene,[1] the more rapid reactions have the higher values of E_0, interpreted for styrene in terms of monomer-acid complex formation.[3]

For the trichloroacetic acid–ethyl bromide system, log $(1/\bar{M}_n)$ is linear with $1/T$, and a value for E_n for $-4{\cdot}5$ kcal. mole^{-1} is obtained. This is normally identified as the difference between the energy of activation for chain propagation and chain breaking, and the value for α-methylstyrene is much greater than that for styrene [1] ($-0{\cdot}85$ kcal. mole^{-1}). This means that at low temperatures high-molecular weight poly-α-methylstyrene can be obtained.

Consumption of the Acid Catalysts.—The acids are consumed during polymerisation to a much larger extent that is to be expected from the incorporation of catalyst fragments in the polymer. Fig. 3 shows a typical acid-consumption curve. Initially the acid is consumed rapidly, but the proportionate consumption of acid falls as reaction proceeds and eventually actual regeneration of acid takes place. This behaviour is more extreme than that of styrene, for which the final regeneration of acid did not occur.[1] The initial rapid consumption of acid is best ascribed, as for styrene, to monomer–acid complex formation.

The consumption of acid at the beginning of the reaction is more marked for trichloroacetic acid. Table 10 shows the initial rates of catalyst consumption for four systems. For reactions in the absence of solvent

$$-d[C]_0/dt = k_0'[C]_0$$

$k_0' = 0{\cdot}060$ and $0{\cdot}015$ for trichloroacetic and dichloroacetic acids respectively. For ethylene dichloride solutions, the ratio $-d[M]_0/dt/-d[C]_0/dt$ is constant, approximately

TABLE 10. *Initial rate of catalyst consumption (mole l.$^{-1}$ min.$^{-1}$, 25°).*

System	$[M]_0$	$[C]_0$	$-d[M]_0/dt$	$-d[C]_0/dt$	$\frac{-d[C]_0/dt}{[C]_0}$	$\frac{-d[M]_0/dt}{-d[C]_0/dt}$
$CCl_3{\cdot}CO_2H$–no solvent	4·40	1·41	0·217	0·094	0·067	—
	5·80	1·10	0·058	0·065	0·059	—
	6·50	0·47	0·0057	0·028	0·060	—
$CHCl_2{\cdot}CO_2H$–no solvent ...	5·20	3·50	0·165	0·050	0·0143	—
	6·00	1·97	0·0394	0·029	0·0147	—
	6·70	1·51	0·0222	0·028	0·0185	—
$CCl_3{\cdot}CO_2H$–$C_2H_4Cl_2$	1·66	1·41	0·0605	0·055	—	1·1
	2·18	0·87	0·0407	0·034	—	1·2
	3·00	0·55	0·0308	0·024	—	1·3
$CHCl_2{\cdot}CO_2H$–$C_2H_4Cl_2$	1·70	2·16	0·0142	0·0080	—	1·8
	2·70	1·61	0·0206	0·010	—	2·0
	2·90	0·86	0·0062	0·0030	—	2·1

unity for trichloroacetic acid, and 2 for dichloroacetic acid catalysis. Hence, for ethylene dichloride solutions,

$$-d[C]_0/dt = k_0'[M]_0^2[C]_0^2$$

with $k_0' = 1{\cdot}1 \times 10^{-2}$ and $0{\cdot}5 \times 10^{-3}$ for trichloroacetic acid and dichloroacetic acid catalysis respectively.

This is a more extended study of the initial rate of acid consumption than was made for styrene.[3] It does not permit conclusions to be drawn concerning the stoicheiometric formulæ of the monomer–catalyst complexes, and so the formulæ suggested for them in the case of styrene [3] must be accepted with reserve. The high initial rates of acid consumption, the high kinetic orders with respect to acid, and the increase of activation energy with reaction rate still require the postulate of monomer–catalyst complex formation however. Acid concentration cannot be determined by titration for the nitromethane solutions.

Internal Order of Reaction Curves.—Some typical reactions were analysed to high degrees of conversion, and the "internal" kinetic orders obtained compared with

TABLE 11. *Reaction rate at 50% polymerisation (25°) (mole l.$^{-1}$ sec.$^{-1}$).*

Medium	$10^4(-d[M]_0/dt)$ (initial rate)	$10^4(-d[M]_{\frac{1}{2}}/dt)$ (rate at 50% polymn.)	$\frac{-d[M]_{\frac{1}{2}}/dt}{-d[M]_0/dt}$ (found)	$\frac{-d[M]_{\frac{1}{2}}/dt}{-d[M]_0/dt}$ (calc.)
α-Methylstyrene–no solvent...	10·8	5·00	0·463	0·215
	0·217	0·108	0·498	0·215
	4·00	1·84	0·460	0·215
α-Methylstyrene–$CH_3{\cdot}NO_2$ ...	0·234	0·0683	0·292	0·240
	0·184	0·045	0·245	0·240
	0·817	0·217	0·266	0·240
Styrene–no solvent	2·67	1·05	0·393	0·215
	1·38	0·567	0·410	0·215
Styrene–$CH_3{\cdot}NO_2$	0·267	0·085	0·318	0·240
	0·484	0·128	0·265	0·240
	0·183	0·058	0·317	0·240

the kinetic orders from the initial rates. The rate of reaction at 50% polymerisation ($-d[M]_{\frac{1}{2}}/dt$) was determined and compared with that calculated from the kinetic order as determined by the initial rates. For the calculation only catalyst

permanently removed from the reaction by combination into the polymer was regarded as consumed. The comparison was made for some of the styrene polymerisations [1] also, and the results are shown in Table 11. Comparison of the ratio of the rate at 50% polymerisation calculated from the kinetic order of the initial rate to the initial rate (column 5), with the ratio of the measured rate at 50% polymerisation to the initial rate (column 4) shows that, while they are in approximate agreement for nitromethane solutions, in the absence of solvent the measured values are approximately double that calculated. The " internal " kinetic order for nitromethane solutions is the same as that derived from the initial rates. In the absence of solvent the rate at 50% conversion is nearly half the initial rate, implying that the rate of reaction is dependent on a lower power of [M] and

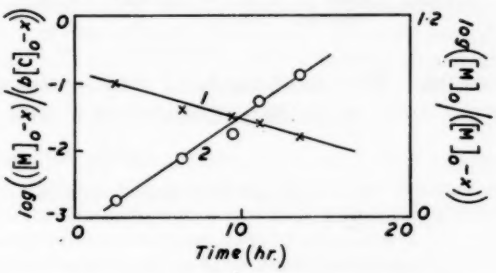


FIG. 4. *Internal order of reaction for trichloroacetic acid catalysis in ethylene dichloride solution* (25°).

1, $\log [([M]_0 - x)/(b[C]_0 - x)]$; 2, $\log [[M]_0/([M]_0 - x)]$.

[C] than is the initial rate. If the internal order was $-d[M]/dt = k[M][C]$, then, if x is the amount of monomer polymerised at time t, and b is the ratio of monomer to catalyst molecules combined in the polymer,

$$-d[M]/dt = k([M]_0 - x)([C]_0 - x/b)$$

and $\log [([M]_0 - x)/(b[C]_0 - x)]$ should be linear in t. This holds for reactions in absence of solvent (Fig. 4). Since $b[C]_0 \gg x$, the consumption of catalyst has relatively little influence on the internal rate, and $\log [[M]_0/([M]_0 - x)]$ is also linear in t (Fig. 4). The internal rate therefore depends on the first power of the monomer concentration but the dependence on catalyst concentration cannot be accurately obtained. It may be that, in non-polar media only, the rate of initiation becomes independent of monomer concentration after the initial stages of the reaction are over.

EXPERIMENTAL

Materials were purified as already described [1,5] and rates were measured by the methods used for styrene [1] except that the sealed-tube technique was always used in preference to the viscosity method. Measurements of residual monomer and acid concentrations, polymer molecular weights, viscosities and infrared spectra were made in the same way as for styrene.[1] Catalytic microhydrogenation was performed with palladium–charcoal. The procedure for the extraction of the polymers has also been described.[5]

Low-molecular weight polymer was fractionated along a horizontal temperature gradient under vacuum (Dainton and Tomlinson [6]). The polymer was contained in a flask connected through a segmented horizontal tube 100 cm. long having a series of constrictions along it to a vacuum pump *via* a liquid-air trap which collected unchanged monomer and solvent still contaminating the polymer. The horizontal tube was surrounded by a jacket containing 4 horizontal heating elements of constantan wound so that the heating decreased along the tube. Two thermometers measured the temperature at the ends of the tube. Asbestos plugs prevented the circulation of air in the jacket. The temperature gradient could be varied from 20—50° to 20—200° with an external resistance. During a few hours the polymer separated into fractions along the horizontal tube, the constrictions facilitating the separate removal of the fractions. The pressure in the apparatus was kept at about 0·5 mm. No degradation or loss of chloroacetate end groups occurred during fractionation.

ERRATA

Part X, *J.*, 1957, 3634, equation (14) *should read* $V_p = -d[M]/dt = k_p k_i K_1[M]^2[C]^2/k_t$.
Part X, *J.*, 1957, 3639, line 17, *for* $E_1 = E_2 + E_3 - E_1$ *read* $E_t = E_2 + E_3 - E_1$.
Part IX, *J.*, 1957, 3629, Table 4, heading, *for* below 30·4° *read* " below −30·4°."

We are indebted to C. R. Davies of the Shell Petroleum Co. in whose laboratory the infrared spectra were measured; to P. H. Plesch for valuable discussions on the interpretation of the spectra; to Mrs. S. M. Bark for the microchemical analysis, and the Salters' Institute of Industrial Chemistry for a scholarship (to C. P. B.).

NOTTINGHAM UNIVERSITY.
[Present Address (A. R. M.).—UNIVERSITY COLLEGE, IBADAN, NIGERIA.]

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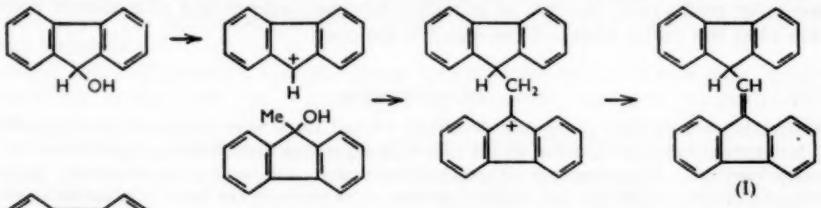
696. *The Acid-catalysed Self-condensation of 9-Methylfluoren-9-ol: 9-Azido-9-methylfluorene and Related Compounds.*

By M. M. COOMBS.

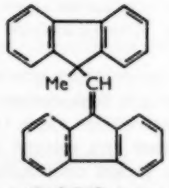
The compound of empirical formula $C_{28}H_{21}N$ formed in the reaction of 9-methylfluoren-9-ol with hydrazoic and sulphuric acid [1] has been shown by synthesis to be (9-methyl-9-fluorenyl)-9-phenanthridinylmethane. This and related reactions, and their mechanisms, are discussed.

WITH hydrazoic and sulphuric acid 9-methylfluoren-9-ol gives 9-methylphenanthridine (47%) and a neutral substance $C_{28}H_{21}N$ (about 25%),[1] whereas 9-ethyl-, 9-*iso*propyl-, and 9-*tert.*-butyl-fluoren-9-ol [2] give the 9-alkylphenanthridines in yields of over 80% if the 9-azido-9-*tert.*-butylfluorene isolated from the last reaction is included. Also fluoren-9-ol itself is converted into phenanthridine in high yield.[3] This anomalous behaviour of the 9-methyl derivative has now been further investigated.

The compound $C_{28}H_{21}N$, m. p. 157°, is insoluble in dilute mineral acids, but forms a 1 : 1 picrate. Its ultraviolet absorption spectrum ($\lambda_{max.}$ 255 mμ, log ε 4·69) is very similar to the algebraic sum ($\lambda_{max.}$ 254 mμ, log ε 4·51) of the spectra of 9-methylfluorene and 9-methylphenanthridine in the 240—280 mμ region; the compound was shown to be



(I)



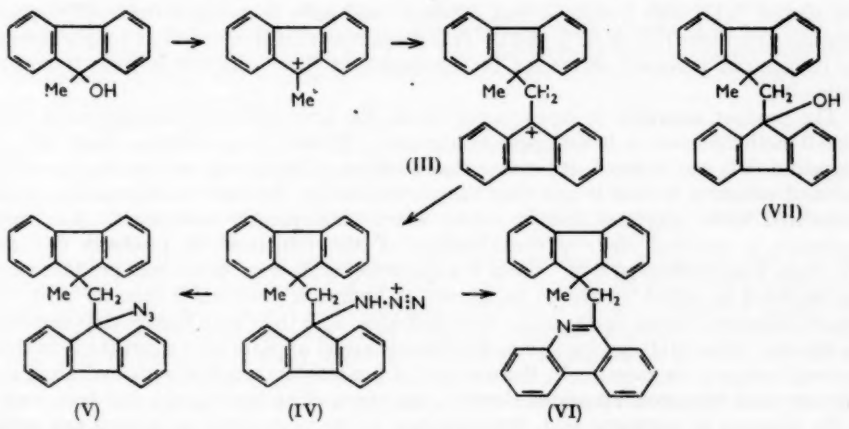
(II)

(9-methyl-9-fluorenyl)-9-phenanthridinylmethane (VI) by synthesis from 9-chloromethylphenanthridine and 9-methyl-9-sodiofluorene. It is not formed from 9-methylfluoren-9-ol by reaction with pre-formed 9-methylphenanthridine in chloroform containing sulphuric or trichloroacetic acid.

[1] Arcus and Coombs, *J.*, 1954, 4319.
[2] Arcus and Lucken, *J.*, 1955, 1634.
[3] Arcus and Mesley, *J.*, 1953, 178.

Wawzonek and Dufek have shown [4] that fluoren-9-ol, when boiled in acetic acid with 9-methylfluoren-9-ol and hydrochloric acid, gives 9-fluorenyl-9-fluorenylidenemethane (I), probably by electrophilic attack by the 9-fluorenyl cation on 9-methylfluoren-9-ol as in acid-catalysed dimerisation of 1 : 1-diphenylethylene.[5] Treating 9-methylfluoren-9-ol alone with acids under various conditions, in the hope of obtaining the 9-methyl homologue (II), gave only a solid of indefinite melting point. It seems nevertheless that self-condensation does occur. Although 9-azido-9-methylfluorene, m. p. 48°, was obtained in high yield when the fluorenol was added gradually to a solution of trichloroacetic and hydrazoic acid in chloroform,[6] a non-basic compound $C_{28}H_{21}N_3$, m. p. 140° (30% yield), was also isolated when the addition was made rapidly. The ultraviolet absorption spectrum of the latter exhibits the bathochromic shift expected for the introduction of a polar azido-group, and a strong infrared band at 2130 cm.$^{-1}$ is characteristic of azides; [7] 9-azido-9-methylfluorene shows a similar band at 2108 cm.$^{-1}$. The structure (9-azido-9-fluorenyl)-(9-methyl-9-fluorenyl)methane (V) is confirmed by synthesis. The condensation between two molecules of 9-methylfluoren-9-ol is presumably followed by reaction of the dimeric cation (III) with hydrazoic acid.

In order to test this reaction sequence (9-hydroxy-9-fluorenyl)-(9-methyl-9-fluorenyl)-methane (VII) was synthesised and its reactions with hydrazoic acid in the presence of (*a*) trichloroacetic and (*b*) sulphuric acid were studied, in the expectation that this alcohol



would ionise to yield the cation (III). 9-Methyl-9-sodiofluorene with methylene dibromide gave 9-bromomethyl-9-sodiofluorene, and from the product of the addition of fluorenone to the derived Grignard reagent was isolated the alcohol (VII), m. p. 203—204°. Its ultraviolet absorption spectrum (cf. Table) showed the expected bathochromic shift and marked lessening of the intensities of the two bands in the 290—300 mμ region, characteristic of fluorenols.[8] The yield of alcohol was very poor (7%); a second substance of m. p. 195°, isolated from the reaction mixture in 11% yield, was an unreactive hydrocarbon $C_{30}H_{26}$, whose ultraviolet absorption spectrum was similar to that of 9 : 9-dimethylfluorene: [9] it is therefore probably 1 : 2-di-(9-methyl-9-fluorenyl)ethane formed by elimination of magnesium bromide between one molecule of Grignard reagent and one molecule

[4] Wawzonek and Dufek, *J. Amer. Chem. Soc.*, 1956, **78**, 3530.
[5] Evans, Jones, and Thomas, *J.*, 1955, 1824; 1956, 2756.
[6] Arcus, Coombs, and Marks, *J.*, 1957, 4064.
[7] Bellamy, "Infra-red Spectra of Complex Molecules," Methuen and Co. Ltd., London, 1954, p. 230.
[8] Friedel and Orchin, "Ultraviolet Spectra of Aromatic Compounds," Chapman and Hall, Ltd., London, 1951.
[9] Greenhow and McNeil, *J.*, 1956, 3208.

of bromomethyl derivative. Treatment of (9-hydroxy-9-fluorenyl)-(9-methyl-9-fluorenyl)-methane (VII) with a chloroform solution of hydrazoic and trichloroacetic acid gave an almost theoretical yield of the azide (V), identical with that isolated as described above.

Absorption spectra [$\lambda_{max.}$ (mμ) and log ε].

(9-Methyl-9-fluorenyl)-9-phenanthridinylmethane	$\lambda_{max.}$	—	255	275	290	305
	log ε	—	4·69	4·27 *	4·00 *	3·95
9-Methylfluorene	$\lambda_{max.}$	—	263	—	290	300
	log ε	—	4·40	—	3·61	3·89
9-Methylphenanthridine	$\lambda_{max.}$	—	249	274	285	—
	log ε	—	4·33	3·68 *	3·43 *	—
(9-Azido-9-fluorenyl)-(9-methyl-9-fluorenyl)methane	$\lambda_{max.}$	—	269	—	287	305
	log ε	—	4·31	—	3·84 *	3·70
(9-Hydroxy-9-fluorenyl)-(9-methyl-9-fluorenyl)-methane	$\lambda_{max.}$	—	269	—	294	305
	log ε	—	4·38	—	3·98 *	3·85
9-Methylfluoren-9-ol	$\lambda_{max.}$	—	274	—	296	303
	log ε	—	4·10	—	3·71	4·32
1 : 2-Di-(9-methyl-9-fluorenyl)ethane	$\lambda_{max.}$	230	263·5	—	291·5	303
	log ε	4·19	4·50	—	4·10	4·32
9 : 9-Dimethylfluorene [9]	$\lambda_{max.}$	228	264	—	296	301·5
	log ε	3·85	4·25	—	3·84	4·05

* Inflection.

The alcohol (VII) with hydrazoic and sulphuric acid gave (9-methyl-9-fluorenyl)-9-phenanthridinylmethane (VI) in 50% yield. It is considered that these results strongly support the mechanism proposed above for the formation of these compounds from 9-methylfluoren-9-ol.

The product normally to be expected [1] from the acid-catalysed rearrangement of 9-azido-9-methylfluorene is 9-methylphenanthridine. However, in addition, about 10% of compound (VI) was isolated, indicating that addition of hydrazoic acid to the 9-methylfluorenyl cation is reversible and that the carbonium ion formed by dissociation of the protonated azide alkylates further azide, which subsequently rearranges. The same conclusion is reached also by consideration of the formation of products (V) and (VI) from 9-methylfluoren-9-ol. Since 9-azido-9-methylfluorene is the sole product when the fluorenol is added slowly to an excess of hydrazoic and trichloroacetic acid, the 9-methylfluorenyl cation reacts faster with hydrazoic acid than with 9-methylfluoren-9-ol; the dimeric cation (III) (giving rise to the dimeric azide) appears only when the 9-methylfluorenyl cation is in excess. In the reaction of 9-methylfluoren-9-ol with hydrazoic and sulphuric acid the alcohol is added slowly to an excess of hydrazoic acid, but here, owing to the presence of sulphuric acid, deprotonation of the protonated azide does not occur. Instead, the reversible nature of the cation–hydrazoic acid reaction provides a small concentration of the 9-methylfluorenyl cation for alkylation leading, *via* (III) and (IV), to (9-methyl-9-fluorenyl)-9-phenanthridinylmethane.

Finally, it was found that treatment of (9-azido-9-fluorenyl)-(9-methyl-9-fluorenyl) methane (V) with sulphuric acid did not yield (9-methyl-9-fluorenyl)-9-phenanthridinylmethane (VI), but products were formed which were not identified but were presumed to be polymeric. There is thus a substantial difference between the course of reaction when (*a*) the protonated azide (IV) is present at relatively low concentration as a reaction intermediate and (*b*) a relatively large concentration of azide (V) is present in equilibrium with its proton-adduct. As deduced in the last section, presumably an equilibrium is set up between the protonated azide (IV) and the corresponding carbonium ion (III), and the latter then attacks unprotonated azide, leading to products containing more than two fluorenyl residues.

Thus the alkylating action of the carbonium ions derived, under appropriate conditions, from both fluorenols and azidofluorenes, leading to substances of molecular size greater than expected, furnishes a consistant account of the products obtained from the above reactions.

XUM

Experimental

98% Sulphuric acid was used throughout.

(9-*Methyl*-9-*fluorenyl*)-9-*phenanthridinylmethane*.—To 9-methyl-9-sodiofluorene (from 1·8 g. of 9-methylfluorene [10]) was added a solution of 9-chloromethylphenanthridine [11] (2·2 g.; m. p. 132°) in dry benzene (25 ml.); the mixture was stirred and heated under reflux for 6 hr. Next day, addition of water to the dark mixture gave an orange benzene solution, which was separated, washed with water, and dried (Na_2SO_4). The oil (3·6 g.) obtained on evaporation mostly dissolved in boiling ethanol (150 ml.) from which were obtained, by successive concentrations, three crops, (i) (0·19 g.), m. p. 225—240°, (ii) (1·10 g.), m. p. 144—148°, (iii) (0·37 g.), m. p. 140—144°. The last two crops were together recrystallised from ethanol four times, yielding needles (0·47 g.), m. p. 157° alone and when mixed with authentic (9-methyl-9-fluorenyl)-9-phenanthridinylmethane.[1]

9-*Bromomethyl*-9-*methylfluorene*.—Methylene dibromide (5·5 ml.) in light petroleum (b. p. 40—60°; 30 ml.) was added to 9-methyl-9-sodiofluorene (from 14·0 g. of 9-methylfluorene), and the mixture was stirred and heated under reflux for 7 hr. under dry nitrogen. Next day the sodium bromide was washed with benzene, and the combined filtrate and washings were evaporated. The residual brown oil was distilled at 138—140°/0·2 mm. (9·5 g.) and crystallised. Recrystallisation from ethanol (25 ml.) gave prisms (6·4 g.) of 9-*bromomethyl*-9-*methylfluorene*, m. p. 59—60° (Found: C, 66·2; H, 4·85; Br, 28·9. $C_{15}H_{13}Br$ requires C, 65·95; H, 4·65; Br, 29·3%).

(9-*Hydroxy*-9-*fluorenyl*)-(9-*methyl*-9-*fluorenyl*)*methane*.—9-Bromomethyl-9-methylfluorene (2·75 g.) and magnesium turnings (0·25 g.) in dry ether (150 ml.) were boiled under reflux for 10 hr. and left overnight. To the Grignard solution (which still contained a little unchanged magnesium) was added dropwise, with stirring, a solution of fluorenone (1·80 g.) in dry ether (50 ml.). After being heated under reflux for 4 hr., the mixture was decomposed with ice and ammonium chloride. The organic layer afforded a yellow oil (3·8 g.) which, crystallised twice from ethanol, formed prisms (0·4 g.), m. p. 194—195°, of 1 : 2-*di*-(9-*methyl*-9-*fluorenyl*)*ethane* (Found: C, 93·3; H, 6·6. $C_{30}H_{26}$ requires C, 93·25; H, 6·75%). This compound was insoluble in, and imparted no colour to, concentrated sulphuric acid.

Evaporation of the original ethanolic filtrate gave a second substance (1·18 g. from 2 batches), melting between 160° and 200°, which on recrystallisation from carbon tetrachloride (75 ml.) yielded small prisms (0·49 g.), m. p. 203—204°, of (9-*hydroxy*-9-*fluorenyl*)-(9-*methyl*-9-*fluorenyl*)-*methane* (Found: C, 90·35; H, 6·1. $C_{28}H_{22}O$ requires C, 89·9; H, 5·9%).

This alcohol (375 mg.) was added gradually during 20 min. at 25° to a stirred mixture of sodium azide (100 mg.), sulphuric acid (0·40 ml.), and chloroform (2·0 ml.); the sulphuric acid layer became deep red. After a further 20 min. at 25° water (20 ml.) was added giving a green oil and a yellow chloroform solution. The latter was separated, combined with further chloroform extracts, washed with water, and dried (Na_2SO_4); evaporation left a brown resin (275 mg.) which, from ethanol, gave crops (i) (70 mg.) m. p. 154—155°, and (ii) (120 mg.) m. p. 150—152°, the former melting at 155—157° when mixed with authentic (9-methyl-9-fluorenyl)-9-phenanthridinylmethane.

9-*Azido*-9-*methylfluorene*.—A mixture of trichloroacetic acid (40 g.), chloroform (50 ml.), and sodium azide (4·0 g.) was stirred at 20° for 15 min., and the temperature was then raised to 30°. 9-Methylfluoren-9-ol (6·0 g.), in chloroform (70 ml.), was added during 40 min. and stirring was continued for 2 hr. longer. Water was added, and the chloroform solution was washed free from acid with water, dried (Na_2SO_4), and evaporated at 40° *in vacuo*, giving a yellow oil which was dissolved in light petroleum (b. p. 40—60°; 10 ml.). There separated columns (5·35 g.) of 9-*azido*-9-*methylfluorene*, m. p. 48—49° (Found: C, 75·05; H, 4·85; N, 18·55. $C_{14}H_{11}N_3$ requires C, 76·0; H, 5·0; N, 19·0%).

A solution of this azide (1·0 g.) in chloroform (5 ml.) was added dropwise to stirred sulphuric acid (2 ml.) and chloroform (10 ml.) during 30 min. at 20°. The red colour which appeared at each fresh addition of azide rapidly became green. The non-basic, chloroform-insoluble solid which separated when the mixture was poured into water was collected; it (295 mg.) was infusible and insoluble in the usual organic solvents. Evaporation of the chloroform solution and recrystallisation of the residue from ethanol gave (9-methyl-9-fluorenyl)-9-phenanthridinylmethane (100 mg.), m. p. 150° (mixed m. p. 154—156°). On neutralisation of the sulphuric acid

[10] Greenhow, McNeil, and White, *J.*, 1952, 986.
[11] Morgan and Walls, *J.*, 1931, 2450.

solution 9-methylphenanthridine (440 mg.), m. p. 82—84°, was obtained. From a second experiment in which the addition was made during 10 min. the yields were: infusible solid (190 mg.), (9-methyl-9-fluorenyl)-9-phenanthridinylmethane (70 mg.), m. p. 152—156°, and 9-methylphenanthridine (520 mg.), m. p. 84°.

(9-*Azido*-9-*fluorenyl*)-(9-*methyl*-9-*fluorenyl*)*methane*.—(a) *From* 9-*methylfluoren*-9-*ol*. 9-Methylfluoren-9-ol (2·0 g.), trichloroacetic acid (10 g.), chloroform (10 ml.), and sodium azide (1·3 g.) were stirred together at 30° for 2 hr., then poured into water. The organic layer afforded, as above, a yellow oil which partly crystallised. The crystals (0·66 g.) were collected, washed with light petroleum, and recrystallised from ethanol (50 ml.). (9-*Azido*-9-*fluorenyl*)-(9-*methyl*-9-*fluorenyl*)*methane* formed tablets (0·40 g.), m. p. 140° (Found: C, 83·9; H, 5·5; N, 9·9. $C_{28}H_{21}N_3$ requires C, 84·2; H, 5·3; N, 10·5%).

(b) *From* (9-*hydroxy*-9-*fluorenyl*)-(9-*methyl*-9-*fluorenyl*)*methane*. This alcohol (22 mg.) was added during 10 min. to a stirred mixture of trichloroacetic acid (200 mg.), chloroform (0·2 ml.), and sodium azide (30 mg.) at 25°. After a further 1½ hr. water and more chloroform were added, and the organic layer was separated, washed with water, and evaporated, yielding a crystalline mass (20 mg.), m. p. 138—139°. Recrystallisation of this azide from ethanol (1 ml.) gave needles (16 mg.), m. p. and mixed m. p. 139—140°.

This azide (1·0 g.) was treated with hydrazoic and sulphuric acid in chloroform, as described for 9-azido-9-methylfluorene (above). The white solid that separated when the mixture was poured into water was collected; it (0·40 g.) was infusible and insoluble in the usual organic solvents. The aqueous and the chloroform layer were separated. The latter, on evaporation, gave a brown solid (0·55 g.), which was infusible and insoluble in ethanol.

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King's College, Strand, London, W.C.2.
(Present address: Imperial College of Science and Technology, London, S.W.7.)

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697. *Aza-steroids. Part I. 3-Aza-A-homo-5α- and -5β-cholestane.**

By C. W. Shoppee and J. C. P. Sly.

5α-Cholestan-3-one oxime undergoes the Beckmann change to give a single ε-lactam, reduced by lithium aluminium hydride to the parent base 3-aza-A-homo-5α-cholestane. The structures of the ε-lactam and the base are proved by conversion of the former into the known related ε-lactone.

5β-Cholestan-3-one oxime similarly yields a single ε-lactam, reduced by lithium aluminium hydride to the parent base 3-aza-A-homo-5β-cholestane. The structures of this ε-lactam and this base are proved by transformation of the former into the ε-lactone and reduction of this with lithium aluminium hydride to 2 : 3-*seco*-5β-cholestane-2 : 3-diol, which we have prepared from 2 : 3-*seco*-5β-cholestane-2 : 3-dioic acid.

The infrared absorption spectra of the ε-lactams suggest that the seven-membered heterocyclic ring A is strainless.

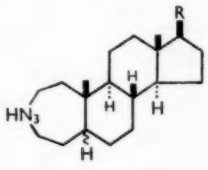
The interesting physiological properties of steroid alkaloids have directed attention to amino-steroids, and numerous papers on the preparation and properties of these compounds have been published.[1] In 1954 we commenced a general study of aza-steroids, with the nitrogen incorporated into ring A, B, C, or D, and embracing the eight series of compounds derived from cholestane, cholane, pregnane, and androstane. We now record

* In this paper acceptance of recent I.U.P.A.C. recommendations is anticipated: the names 5α-cholestane, 5β-cholestane, and 5β-cholane are used in place of cholestane, coprostane, and cholane, respectively (*J.*, 1951, 3527).

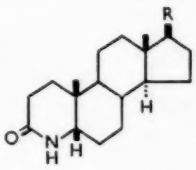
[1] *E.g.*, Barnett, Ryman, and Smith, *J.*, 1946, 524, 526, 528; Uhle, *J. Amer. Chem. Soc.*, 1951, **73**, 883; Howarth, McKenna, and Powell, *J.*, 1952, 1110; Šorm, Labler, and Czerny, *Coll. Czech. Chem. Comm.*, 1953, **12**, 842; Fieser and Huang, *J. Amer. Chem. Soc.*, 1953, **75**, 6306; Gould, Shapiro, and Hershberg, *ibid.*, 1954, **76**, 5567; Micheli and Bradsher, *ibid.*, 1955, **77**, 4788.

the preparation of two of the parent bases, 3-aza-A-homo-5α- and -5β-cholestane (as I; R = C_8H_{17}).

Barnett and Reichstein [2] prepared a compound which they regarded as the 24→12-lactam of a methyl 12-amino-11-hydroxy-5β-cholanate, but before our work few communications dealing with aza-steroids have appeared. W. E. Bachmann and Ramirez [3]



(I)



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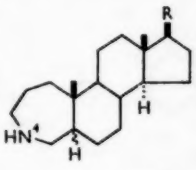


(III)

have described the 16-aza-17-oxosteroids derived from (±)-3-deoxyequilenin and (±)-3-deoxy-14-*iso*equilenin; Kaufmann [4] prepared single 17-oxo-17*a*-aza-D-homosteroids from the oximes of dehydro*epi*androsterone, of androst-4-ene-3 : 17-dione, and of (±)-œstrone-*b* benzoate by Beckmann rearrangement; Woodward *et al.*[5] obtained the 4-phenyl and the 4-benzyl derivative of 4-azacholest-5-en-3-one as by-products of their total synthesis of cholesterol; and Clemo and Mishra [6] synthesised 4-aza-1 : 2-*cyclo*pentenophenanthrene from α-naphthylamine and ethyl 2-oxo*cyclo*pentanecarboxylate.

Since our work, Hara [7] has prepared, by essentially the method we used, methyl 4-oxo-3-aza- and 3-oxo-4-aza-5β-cholanate (II; R = $C_4H_8{\cdot}CO_2Me$) and methyl 3-oxo-4-aza- and 4-oxo-3-aza-A-homo-5β-cholanate; by reduction of the latter pair of esters with lithium aluminium hydride, he obtained 3-aza-A-homo-5β-cholan-24-ol (I; R = $C_4H_8{\cdot}CH_2{\cdot}OH$) and 4-aza-A-homo-5β-cholan-24-ol (III; R = $C_4H_8{\cdot}CH_2{\cdot}OH$). The structure of the 4-aza-steroid was established by conversion into 1-azachrysene,[8] whilst that of the 4-aza-A-homosteroid was proved by acid hydrolysis, Hofmann degradation, and ozonolysis to the known 5-oxo-3 : 4-*seco*-A-norcholanic acid; the structures of the corresponding 3-aza-steroids, which were obtained only in traces (1%, 3%), follow by exclusion. By similar reactions Regan and Hayes [9] recently prepared single 17-oxo-17*a*-D-homosteroids from the oximes of dehydro*epi*androsterone acetate and of (+)-œstrone-*b* and its methyl ether by Beckmann rearrangement, and, by reduction with lithium aluminium hydride, the corresponding 17*a*-aza-steroids; structures were assigned on the basis of the ease of esterification of the amino-acids derived by alkaline hydrolysis of the 17-oxo-17*a*-aza-D-homosteroids.

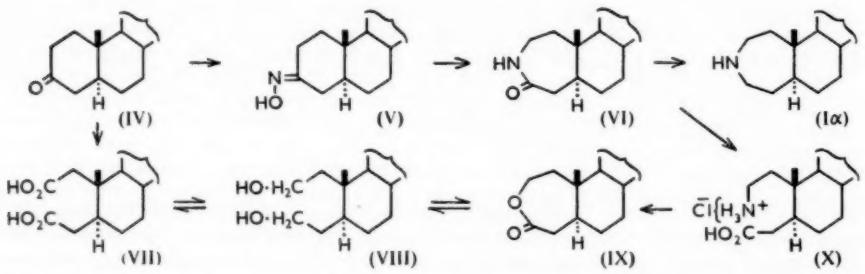
5α-Cholestane-3-one (IV) gives a single oxime (V), which by treatment with thionyl chloride in dioxan undergoes the Beckmann change to yield the ε-lactam (VI); this, by reduction with lithium aluminium hydride, gives 3-aza-A-homo-5α-cholestane (Iα; R = C_8H_{17}), which was characterised by preparation of the *N*-acetyl derivative, the nitrosamine, and the *N*-methyl methiodide.

The structures of the ε-lactam (VI) and the base (Iα) have been proved in the following way. The ε-lactam by hydrolysis with hydrochloric–acetic acid furnishes the amino-acid hydrochloride (X), deaminated by nitrous acid to the analogous hydroxy-acid, which immediately forms the ε-lactone (IX), m. p. 185°, $[\alpha]_D$ +46°. This ε-lactone is identical with that obtained by Nes and Lettré [10] by chromium trioxide oxidation of the diol (VIII),

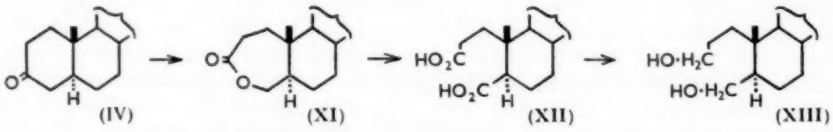
[2] Barnett and Reichstein, *Helv. Chim. Acta*, 1938, **21**, 926.
[3] W. E. Bachmann and Ramirez, *J. Amer. Chem. Soc.*, 1950, **72**, 2527.
[4] Kaufmann, *ibid.*, 1951, **73**, 1779.
[5] Woodward, Sondheimer, Taub, Heusler, and McLamore, *ibid.*, 1952, **74**, 4230.
[6] Clemo and Mishra, *J.*, 1953, 192.
[7] Hara, *Pharm. Bull.* (*Japan*), 1955, **3**, 209, 297.
[8] Mosettig and Krueger, *J. Org. Chem.*, 1938, **3**, 325.
[9] Regan and Hayes, *J. Amer. Chem. Soc.*, 1956, **78**, 639; cf. ref. 4.
[10] Nes and Lettré, *Annalen*, 1956, **598**, 65.

m. p. 156°, which they prepared by reduction with lithium aluminium hydride of the anhydride or the dimethyl ester of the Windaus–Uibrig acid [11] (VII).

The ε-lactone (IX) is different from the isomeride (XI), m. p. 186°, $[\alpha]_D$ +1°, +4°, prepared by Burckhardt and Reichstein [12] and by us from 5α-cholestan-3-one (IV) by oxidation with perbenzoic acid in chloroform at 20°, whose structure is proved by alkaline



hydrolysis to the corresponding hydroxy-acid and oxidation of this as the methyl ester with chromium trioxide in acetic acid at 20° to give, after alkaline hydrolysis, dihydro-Diels's acid [11] (XII). Finally, the ε-lactone (XI), by reduction with lithium aluminium hydride, gives the diol (XIII), m. p. 121°, $[\alpha]_D$ +10°, which is different from the isomeride (VIII).



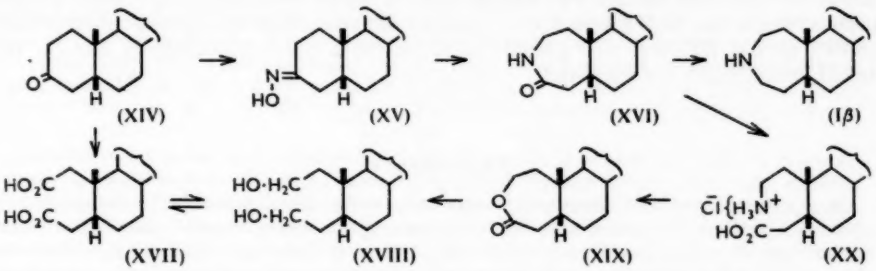
Gardner and Ellis,[13] on protracted oxidation of 5α-cholestan-3-one (IV) with ammonium persulphate in acetic acid at 80°, isolated three lactones, $C_{27}H_{46}O_2$, m. p. 159°, 201°, and 184°. The nature of the second compound is obscure; the first is probably identical with the lactone, m. p. 154—155°, $[\alpha]_D$ +28°, prepared by Nes [14] by oxidation of 2 : 3-*seco*-5α-cholestane-2 : 3-diol (VIII) with chromium trioxide in acetic acid—whereby oxidation of the primary 2-alcohol group, as opposed to the primary 3-alcohol group, has occurred. The third compound, for which no specific rotation is recorded, could be identical with either of the lactones (IX) and (XI).

5β-Cholestan-3-one (XIV) affords a single oxime (XV) which, by Beckmann rearrangement with thionyl chloride, gives the ε-lactam (XVI), reduced by lithium aluminium hydride to 3-aza-A-homo-5β-cholestane (Iβ; R = C_8H_{17}), which was characterised as the *N*-acetyl derivative and the *N*-methyl methiodide. The structures (XVI) and (Iβ) rest on the following evidence. The ε-lactam (XVI) by acid hydrolysis yields the amino-acid hydrochloride (XX), deaminated by nitrous acid to the hydroxy-acid which passes into the ε-lactone (XIX), m. p. 183°, $[\alpha]_D$ +50°, reduced by lithium aluminium hydride to the diol (XVIII). The ε-lactone (XIX) was originally obtained by Gardner and Godden [15] from 5β-cholestan-3-one (XVII) as the main product of protracted oxidation with ammonium persulphate in acetic acid at 80°. The diol (XVIII) has also been prepared by us from

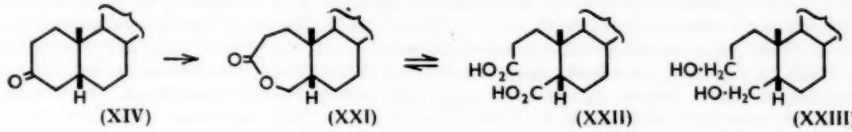
[11] Windaus and Uibrig, *Ber.*, 1914, **47**, 2387; Windaus and Dalmer, *Ber.*, 1919, **52**, 162.
[12] Burckhardt and Reichstein, *Helv. Chim. Acta*, 1942, **25**, 1434.
[13] Gardner and Ellis, *Biochem. J.*, 1918, **12**, 72.
[14] Nes, personal communication.
[15] Gardner and Godden, *Biochem. J.*, 1913, **7**, 588.

XUM

5β-cholestan-3-one (XIV), by conversion into the 2β-sulphonic methyl ester,[16] and oxidation with chromium trioxide in acetic acid at 70° to 2 : 3-*seco*-5β-cholestane-2 : 3-dioic acid [16,17] (XVII), and reduction of this with lithium aluminium hydride.



The ε-lactone (XIX) differs from the isomeride (XXI), m. p. 157°, $[\alpha]_D$ +49°, first obtained by Gardner and Godden [15] from 5β-cholestan-3-one (XIV) by protracted oxidation with ammonium persulphate in acetic acid at 80°; the isomer (XXI) was also prepared by Burckhardt and Reichstein [12] and by us from 5β-cholestan-3-one (XIV) by oxidation with perbenzoic acid in chloroform at 20°, as well as by Lederer *et al.*[18] The structure (XXI) is proved by alkaline hydrolysis to the hydroxy-acid and oxidation of this as the methyl ester with chromium trioxide in acetic acid at 20° to give, after alkaline hydrolysis, Gardner's acid [15,16] (XXII). The ε-lactone (XXI) by reduction with lithium aluminium hydride affords the diol (XXIII), m. p. 124°, $[\alpha]_D$ +35°.



The principal frequencies in the infrared absorption spectra of the ε-lactams (VI, XVI) are here tabulated, together with those for the isomeric ε-lactam esters (as I or III; R = $C_4H_8{\cdot}CO_2Me$) reported by Hara [7] (who does not specify the conditions of observation).

ε-Lactam		Frequencies (cm.$^{-1}$) NH	[NH]–C=O
(VI)	5α	3420	1655
(XVI)	5β	3420	1658
(Cf. I) 4-Oxo-3-aza-	5β	3115, 3224	1645, 1681
(Cf. III) 3-Oxo-4-aza-	5β	3135, 3236	1664, 1669

The NH stretching frequency observed for (VI) and (XVI) at 3420 cm.$^{-1}$ corresponds with the single band shown by simple secondary amides and lactams in dilute solution. The double peaks observed for the isomeric ε-lactams (as I or III; R = $C_4H_8{\cdot}CO_2Me$) suggest that the measurements were made on the compounds in the solid state.

The carbonyl absorption frequencies are similar to those of normal secondary amides (dilute solution, 1670—1700 cm.$^{-1}$; solid, 1630—1680 cm.$^{-1}$) and comparable with the value 1667 cm.$^{-1}$ for a nine-membered ring lactam reported by Witkop *et al.*[19] This suggests that the seven-membered rings are unstrained.* Accurate models indicate that,

* The ε-lactone (IX) and its isomeride,[14] m. p. 155°, $[\alpha]_D$ +28°, are also strainless, exhibiting $\nu_{max.}$ 1742—1746 cm.$^{-1}$ in CS_2.

[16] Windaus and Kuhr, *Annalen*, 1937, **532**, 52; Windaus and Mielke, *ibid.*, 1938, **536**, 116.
[17] Marker, Wittle, Plambeck, Rohrmann, Krueger, and Ulshafer, *J. Amer. Chem. Soc.*, 1939, **61**, 3317.
[18] Lederer, Marx, Mercier, and Perot, *Helv. Chim. Acta*, 1946, **29**, 1354.
[19] Witkop, Patrick, and Rosenblum, *J. Amer. Chem. Soc.*, 1951, **73**, 2641.

in the A/B-*trans*-compound (VI), ring A is strainless and can exist in various conformations capable of strainless interconversion; in one of these the mutual repulsion of 1α- and 5α-H is minimised at the expense of approach by 2β- and 4*a*β-H, whilst in another 2β- and 4*a*β-H are virtually parallel and almost axial, although rotation of $C_{(1)}$ causes a slight increase in the 1α-, 5α-H interaction. A similar situation holds for the A/B-cis-compounds (XVI: as I or III), with one possible conformation in which 2β- and 5β-H, and 1α- and 4*a*α-H, respectively, are staggered.

Experimental

M. p.s were determined thermoelectrically on a Kofler block (error ±2°). Solvents were rigorously purified and dried and, for chromatography, unless stated otherwise, alumina (Spence type H, activity ~ II) was used. The " usual working up " implies extraction with ether, washing the ethereal extract successvely with 2N-sodium carbonate and water, brief drying (Na_2SO_4), and evaporation. $[\alpha]_D$ are for $CHCl_3$ solutions unless otherwise stated. Ultraviolet absorption spectra were determined for EtOH solutions in a Hilger Uvispek spectrophotometer, whilst infrared absorption spectra were measured for CCl_4 solutions on a Perkin-Elmer Model 21 double-beam instrument, unless otherwise specified.

Beckmann Rearrangement of 5α-Cholestan-3-one Oxime.—5α-Cholestan-3-one oxime (4·8 g.) in dry dioxan (150 c.c.) was warmed to 40° and thionyl chloride (4·5 c.c.) added with stirring during 5 min. The mixture was kept at 40° for a further 10 min., then made alkaline by saturated sodium hydrogen carbonate solution. The mixture was further diluted with water and extracted with much ether. Working up in the usual manner furnished a solid (4·5 g.), which was chromatographed on aluminium oxide (130 g.) prepared in benzene. Elution with benzene (3 × 450 c.c.) and ether–benzene (1 : 4; 3 × 450 c.c.) furnished a sticky solid; elution with ether–benzene (1 : 1; 5 × 450 c.c.) and ether (5 × 450 c.c.) gave unchanged oxime (930 mg.); elution with ether–chloroform (1 : 1; 2 × 450 c.c.) and chloroform (3 × 450 c.c.) gave 3-*aza*-A-*homo*-5α-*cholestan*-4-*one* (VI) (3·0 g.), which after sublimation at 200—220°/0·02 mm. had m. p. 268—271°, $[\alpha]_D$ +16° (*c* 0·7) (Found: C, 80·8; H, 11·8; N, 3·5. $C_{27}H_{47}ON$ requires C, 80·7; H, 11·8; N, 3·5%).

Lithium Aluminium Hydride Reduction of 4-*Oxo*-3-*aza*-A-*homo*-5α-*cholestane* (VI).—The lactam (1 g.) in dioxan (150 c.c.) was refluxed for 48 hr. with lithium aluminium hydride (1 g.). Excess of hydride was destroyed with water. Repeated extraction of the precipitated aluminium hydroxide with chloroform, followed by evaporation of solvent, gave an oil (950 mg.) which, by treatment with dry hydrogen chloride in ether, gave the insoluble 3-*aza*-A-*homo*-5α-*cholestane hydrochloride*, which crystallised from methanol–ethyl acetate, m. p. 275—280° [Found (after drying at 120°/0·5 mm. for 4 hr.): C, 76·25; H, 11·8. $C_{27}H_{50}NCl$ requires C, 76·4; H, 11·9%]. The hydrochloride with 4N-methanolic potassium hydroxide gave 3-*aza*-A-*homo*-5α-*cholestane* (Iα), b. p. 230—235°/0·7 mm., $[\alpha]_D$ +52° (*c* 0·8), which could not be satisfactorily crystallised (Found: C, 83·3; H, 12·8. $C_{27}H_{49}N$ requires C, 83·6; H, 12·75%). With acetic anhydride–pyridine at 100° for 6 hr. it gave, after crystallisation from aqueous acetone, N-*acetyl*-3-*aza*-A-*homo*-5α-*cholestane*, m. p. 109—111°, $[\alpha]_D$ +50° (*c* 0·8) [Found (after distillation at 235—240°/0·4 mm.): C, 80·5; H, 12·3. $C_{29}H_{51}ON$ requires C, 81·0; H, 11·8%].

N-*Nitroso*-3-*aza*-A-*homo*-5α-*cholestane*.—The aza-steroid, on treatment with sodium nitrite solution in boiling acidic aqueous dioxan, gave N-*nitroso*-3-*aza*-A-*homo*-5α-*cholestane*, m. p. 107—109°, after crystallisation from acetone [Found (after drying at 25°/0·4 mm. for 10 hr.): C, 77·5; H, 11·5. $C_{27}H_{48}ON_2$ requires C, 77·8; H, 11·6%].

N-*Methyl*-3-*aza*-A-*homo*-5α-*cholestane Methiodide*.—The aza-steroid (100 mg.) was heated at 100° for 3 hr. with 99% formic acid (1 c.c.) and 40% formaldehyde (1 c.c.). The mixture was poured into water, basified with ammonia, and extracted with ether. The ethereal solution was washed with water, dried, and evaporated to an oil; this was dissolved in acetone (3 c.c.), methyl iodide (0·3 c.c.) added, and the mixture refluxed for 0·5 hr. Evaporation and trituration of the residual solid with ether gave N-*methyl*-3-*aza*-A-*homo*-5α-*cholestane methiodide*, m. p. 275—277° after crystallisation from methanol–ethyl acetate [Found (after drying at 95°/0·4 mm. for 5 hr.): C, 63·7; H, 9·8; N, 2·7. $C_{28}H_{54}NI$ requires C, 64·0; H, 10·0; N, 2·6%].

Acid Hydrolysis of 3-*Aza*-A-*homo*-5α-*cholestan*-4-*one* (VI).—The lactam (1·5 g.) was refluxed

with acetic acid (300 c.c.) and concentrated hydrochloric acid (75 c.c.) for 40 hr., during which a slow stream of hydrogen chloride was passed through the solution. The solution was evaporated to dryness under reduced pressure. The residual solid was triturated with methanol–water (5 : 1), and the insoluble starting material (0·4 g.) removed. The aqueous methanol solution was evaporated almost to dryness; then a further quantity of unchanged lactam (0·1 g.) was removed. Evaporation of the methanol solution to dryness and crystallisation of the solid product from methanol–ethyl acetate gave *2-amino-2 : 3-seco-5α-cholestan-3-oic acid hydrochloride* (X) (1·2 g.), m. p. 220—225° [Found (after drying at 70°/0·5 mm. for 4 hr.): C, 67·8; H, 10·7; N, 2·9. $C_{27}H_{50}O_2NCl,CH_3{\cdot}CO_2Et$ requires C, 68·3; H, 10·7; N, 2·9%].

Deamination of 2-Amino-2 : 3-seco-5α-cholestan-3-oic Acid Hydrochloride (X): *2-Hydroxy-2 : 3-seco-5α-cholestan-3-oic* 3 ⟶ *2-Lactone* (IX).—The hydrochloride (550 mg.) in 55% acetic acid (130 c.c.) was treated with an ice-cold solution of sodium nitrite (1·1 g.) in 55% acetic acid (20 c.c.), shaken intermittently for 1 hr., and left at 15° for a further 40 hr. It was diluted with water, shaken with ether, and filtered, to remove unchanged hydrochloride (220 mg.). The ethereal solution was washed repeatedly with water, dried, and evaporated to a solid (270 mg.), m. p. 175—183°, which was chromatographed on neutral aluminium oxide [20] (8 g.) prepared in benzene–pentane (1 : 1). Elution with benzene (4 × 30 c.c.) gave, after crystallisation from ether–methanol, the lactone (IX) (130 mg.), m. p. 181—183°, $[\alpha]_D$ +46° (*c* 0·7), $\nu_{max.}$ (in CS_2) 1746 cm.$^{-1}$ (CO) (absence of OH band) [Found (after drying at 20°/0·02 mm. for 4 hr.): C, 80·3; H, 11·4. Calc. for $C_{27}H_{46}O_2$: C, 80·5; H, 11·4%], which gave no m. p. depression with an authentic specimen of m. p. 184—185°, $[\alpha]_D$ +47°, $\nu_{max.}$ (in CS_2) 1742, 1744 cm.$^{-1}$, prepared by Nes and Lettre.[10,14]

3-Hydroxy-2 : 3-seco-5α-cholestan-2-oic 2 ⟶ *3-Lactone* [*by* Dr. W. R. Nes].—Modification of the procedure of Nes and Lettré [10] for oxidation of the diol (VIII), by use of chromium trioxide in acetic acid, affords *3-hydroxy-2 : 3-seco-5α-cholestan-2-oic* 2 ⟶ *3-lactone*, m. p. 154—155°, $[\alpha]_D$ +28°, $\nu_{max.}$ (in CS_2) 1742 cm.$^{-1}$ [absence of OH band, differences from (IX) in the finger-print region] (Found: C, 80·5; H, 11·4. $C_{27}H_{46}O_2$ requires C, 80·6; H, 11·4%).

4-Hydroxy-3 : 4-seco-5α-cholestan-3-oic 3 ⟶ *4-Lactone* (XI).—5α-Cholestan-3-one (1·2 g.) was treated with a chloroform solution of perbenzoic acid (23 c.c.; 1 c.c. = 52·5 mg. of perbenzoic acid) at 15°, and the solution kept in the dark for 16 hr. Excess of perbenzoic acid was destroyed with potassium iodide solution, and free iodine destroyed with sodium thiosulphate solution. The usual isolation procedure, with washing with sodium hydrogen carbonate solution gave, after crystallisation from ether–methanol, 4-hydroxy-3 : 4-*seco*-5α-cholestan-3-oic 3 ⟶ 4-lactone (XI), m. p. 186°, $[\alpha]_D$ +4° (*c* 1·2) {lit.,[12] m. p. 186—187°, $[\alpha]_D$ +1° (in acetone)}.

3 : 4-seco-5α-*Cholestane-3 : 4-diol* (XIII).—4-Hydroxy-3 : 4-*seco*-5α-cholestan-3-oic 3 ⟶ 4-lactone (XI) (150 mg.) in ether (35 c.c.) was refluxed with lithium aluminium hydride (50 mg.) for 1 hr. Excess of hydride was destroyed with ethyl acetate, and the mixture worked up in the usual way to give, after crystallisation from acetone, 3 : 4-seco-5α-*cholestane-3 : 4-diol* (110 mg.), m. p. 121—122°, $[\alpha]_D$ +10° (*c* 1·0) [Found (after drying at 20°/0·02 mm. for 6 hr.): C, 79·5; H, 12·2. $C_{27}H_{50}O_2$ requires C, 79·7; H, 12·3%].

Beckmann Rearrangement of 5β-Cholestan-3-one Oxime.—5β-Cholestan-3-one oxime (m. p. 65—67°; 4·5 g.) in dry dioxan (200 c.c.) was warmed to 40° and thionyl chloride (10 c.c.) added, with stirring, during 5 min. The mixture was kept at 40° for a further 20 min., cautiously neutralised with saturated sodium hydrogen carbonate solution, and extracted with a large volume of ether. The product, a dark brown oil (4·3 g.), was chromatographed on aluminium oxide (130 g.) prepared in benzene–pentane (1 : 1). Elution with benzene–pentane (1 : 1), benzene, and ether furnished uncrystallisable oils (1·3 g.); elution with chloroform–ether (1 : 4, 3 × 200 c.c.; and 3 : 7, 4 × 200 c.c.) gave *3-aza-A-homo-5β-cholestan-4-one* (XVI) (1·62 g.) which, after sublimation at 190—200°/0·02 mm., had m. p. 166—174° clearing to a homogeneous liquid at 195°, $[\alpha]_D$ +42° (*c* 0·8). Repeated sublimation and crystallisation from methylene chloride failed to alter the m. p. (Found: C, 80·5; H, 11·7; N, 3·45. $C_{27}H_{47}ON$ requires C, 80·7; H, 11·8; N, 3·5%).

Lithium Aluminium Hydride Reduction of 3-Aza-A-homo-5β-cholestan-4-one (XVI).—The ε-lactam (XVI) (1 g.) in dry dioxan (125 c.c.) was refluxed with lithium aluminium hydride (1 g.) for 48 hr. Working up as for the 5α-epimeride (VI) gave (*a*) *3-aza-A-homo-5β-cholestane*

[20] Reichstein and Shoppee, *Trans. Faraday Soc.*, 1949, **7**, 205.

hydrochloride, m. p. 267—271°, after recrystallisation from methanol–ethyl acetate [Found (after drying at 120°/0·5 mm. for 4 hr.): C, 76·1; H, 11·9. $C_{27}H_{50}NCl$ requires C, 76·4; H, 11·9%], (*b*) 3-*aza*-A-*homo*-5β-*cholestane* (Iβ), b. p. 200—210°/0·5 mm., $[\alpha]_D$ +27° (*c* 2·0) (Found: C, 83·4; H, 12·75; N, 3·8. $C_{27}H_{49}N$ requires C, 83·6; H, 12·75; N, 3·6%), and (*c*) N-*acetyl*-3-*aza*-A-*homo*-5β-*cholestane*, m. p. 105—107°, $[\alpha]_D$ +33° (*c* 0·9), after crystallisation from 90% aqueous acetone [Found (after distillation at 250°/0·5 mm.): C, 80·6; H, 11·95. $C_{29}H_{51}ON$ requires C, 81·0; H, 11·95%].

N-*Methyl*-3-*aza*-A-*homo*-5β-*cholestane Methiodide*.—The aza-steroid (Iβ) (100 mg.), 90% formic acid (1 c.c.), and 40% formaldehyde (1 c.c.) were heated together at 100° for 3 hr. The mixture was poured into water, basified with ammonia, and extracted with ether. The ethereal solution was washed with water, dried, and evaporated. The residual oil was dissolved in acetone (5 c.c.), methyl iodide (0·5 c.c.) added, and the mixture refluxed for 0·5 hr.; evaporation of the solvent and washing of the residual solid with ether gave N-*methyl*-3-*aza*-A-*homo*-5β-*cholestane methiodide*, m. p. 280—282°, after crystallisation from methanol–ethyl acetate [Found (after drying at 100°/0·5 mm. for 2 hr.): C, 64·1; H, 9·8; N, 2·5. $C_{28}H_{48}NI$ requires C, 64·1; H, 10·0; N, 2·6%].

Hydrolysis of 3-*Aza*-A-*homo*-5β-*cholestan*-4-*one* (XVI).—A solution of the ε-lactam (1·05 g.) in acetic acid (200 c.c.) and concentrated hydrochloric acid (55 c.c.) was refluxed for 45 hr. The solution was evaporated to dryness under reduced pressure, and the residual solid (1·1 g.) recrystallised from methanol–ether to give 2-*amino*-2 : 3-seco-5β-*cholestan*-3-*oic acid hydrochloride* (XX) (900 mg.), m. p. 223—229° [Found (after drying at 125°/0·03 mm. for 6 hr.): C, 69·85; H, 10·9; N, 3·0. $C_{27}H_{50}O_2NCl$ requires C, 70·1; H, 11·05; N, 3·1%].

Deamination of 2-*Amino*-2 : 3-seco-5β-*cholestan*-3-*oic Acid Hydrochloride* (XX).—The hydrochloride (500 mg.) in 55% acetic acid (100 c.c.) was treated with a cold solution of sodium nitrite (1 g.) in 55% acetic acid (10 c.c.), and the mixture was set aside overnight at 20°. The mixture was diluted with water, extracted with ether, and filtered to remove unchanged hydrochloride. The ethereal extract was repeatedly washed with water until all the unchanged hydrochloride had been removed, dried, and evaporated to give a solid (220 mg.), which was chromatographed on neutralised aluminium oxide [20] (7 g.) prepared in benzene–pentane (1 : 4). Elution with benzene–pentane (1 : 1) afforded, after crystallisation from ether–methanol, 2-*hydroxy*-2 : 3-seco-5β-*cholestan*-3-*oic* 3 ⟶ 2-*lactone* (XIX), m. p. 182—183°, $[\alpha]_D$ +50° (*c* 1·0) [Found (after drying at 20°/0·03 mm. for 4 hr.): C, 80·6; H, 11·4. $C_{27}H_{46}O_2$ requires C, 80·55; H, 11·4%].

Lithium Aluminium Hydride Reduction of 2-*Hydroxy*-2 : 3-seco-5β-*cholestan*-3-*oic* 3 ⟶ 2-*Lactone* (XIX).—(*a*) The ε-lactone (200 mg.) in ether was refluxed with lithium aluminium hydride for 4 hr. The usual working up gave an oil (190 mg.), which was chromatographed on aluminium oxide (6 g.). Elution with methanol (20 c.c. × 4) gave 2 : 3-seco-5β-*cholestane*-2 : 3-*diol* (XVIII) (140 mg.) as a glass, b. p. 160—165°/0·02 mm., $[\alpha]_D$ +26° (*c* 1·4) (Found: C, 79·5; H, 12·2. $C_{27}H_{50}O_2$ requires C, 79·7; H, 12·3%).

(*b*) 2 : 3-*seco*-5β-Cholestane-2 : 3-dioic acid [16] (300 mg.) in ether was refluxed with lithium aluminium hydride for 5 hr. Working up in the usual way gave an oil (280 mg.), which was chromatographed on aluminium oxide (9 g.). Elution with methanol furnished a glass (220 mg.), b. p. 158—164°/0·02 mm., $[\alpha]_D$ +27° (*c*, 1·6), which did not crystallise (Found: C, 79·4; H, 12·3%).

4-*Hydroxy*-3 : 4-seco-5β-*cholestan*-3-*oic* 3 ⟶ 4-*Lactone* (XXI).—5β-Cholestan-3-one (m. p. 60—61°; 1·3 g.) was treated with a chloroform solution of perbenzoic acid (30 c.c.; 1 c.c. ≡ 30 mg. perbenzoic acid), and the solution kept in the dark at 20° for 22 hr. Excess of perbenzoic acid was destroyed with potassium iodide solution, and the resulting iodine removed with sodium thiosulphate solution. Extraction with ether, followed by washing with sodium hydrogen carbonate solution and water, drying, and evaporation, gave 4-hydroxy-3 : 4-*seco*-5β-cholestan-3-oic 3 ⟶ 4-lactone (1 g.), m. p. 158°, $[\alpha]_D$ +49° (*c* 1·2), after crystallisation from methanol.

3 : 4-seco-5β-*Cholestane*-3 : 4-*diol* (XXIII).—4-Hydroxy-3 : 4-*seco*-5β-cholestan-3-oic 3 ⟶ 4-lactone (XXI) (500 mg.) in ether (120 c.c.) was refluxed with lithium aluminium hydride (200 mg.) for 1 hr. Working up in the usual way gave an oil (450 mg.), which crystallised from ether–pentane to give 3 : 4-seco-5β-*cholestane*-3 : 4-*diol*, m. p. 124—126°, $[\alpha]_D$ +35° (*c* 1·0) [Found (after drying at 20°/0·03 mm. for 18 hr.): C, 79·3; H, 12·0. $C_{27}H_{50}O_2$ requires C, 79·7; H, 12·4%].

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UNIVERSITY OF WALES, UNIVERSITY COLLEGE, SWANSEA.
UNIVERSITY OF SYDNEY, DEPT. OF ORGANIC CHEMISTRY. [*Received, April 9th*, 1958.]

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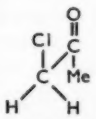
698. *Infrared Spectra and Polar Effects. Part IX.* Field Effects in α-Halogenated Aldehydes and Acid Chlorides.*

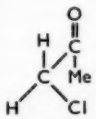
By L. J. BELLAMY and R. L. WILLIAMS.

The effects of α-chlorine substitution in aldehydes and acid chlorides are compared. In aldehydes the most stable rotational isomer is probably that in which the chlorine occupies a position well away from the oxygen atom. This is due to the low steric repulsion of the aldehyde hydrogen atom. In acid chlorides the situation is reversed, as the steric effect is then large and is reinforced by electrostatic repulsions between the chlorine atoms. Some apparently anomalous carbonyl frequencies are observed in the acid halide series and the origin of these is discussed.

SUBSTANTIAL results are now available on the spectroscopic behaviour of α-halogenated ketones: the carbonyl frequency rises when the halogen and oxygen atoms are close together but remains unchanged when they are not.[1] This has been attributed to an intramolecular field effect and many otherwise anomalous frequencies can be satisfactorily explained on this basis. When CH_2Cl or $CHCl_2$ groups are adjacent to the carbonyl group, rotational isomerism leads to two carbonyl absorptions. These can be assigned to the more and the less polar conformation on the basis of the observed frequencies, and the results obtained agree well with previous assignments based on dipole moments and similar results.

In chloroacetone the two conformations are close to (I) and (II), and the carbonyl frequency in the former is raised whilst in the latter it is unchanged. Mizushima *et al.* suggested[2] that the relative stabilities of these conformations are determined by the resultant of the electrostatic repulsion between the oxygen and the chlorine atom which operates in one


(I)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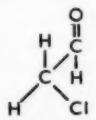
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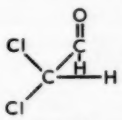
(IV)

direction, and of the steric repulsion between the methyl group and the chlorine atom which operates in the other. We have therefore studied α-chlorinated aldehydes in which the steric repulsion is reduced to a minimum, and α-chlorinated acid chlorides in which the steric effect is much increased and is reinforced by an electrostatic repulsion between the two halogen atoms.

α-Halogenated aldehydes do not appear to have been studied previously, but Mizushima *et al.*[3] discussed the spectra of chloroacetyl chloride, bromoacetyl chloride, and bromoacetyl bromide. On the basis of a normal co-ordinate treatment they conclude that the

* Part VIII, *J.*, 1958, 2463.

[1] Bellamy, Thomas, and Williams, *J.*, 1956, 3704; Bellamy and Williams, *J.*, 1957, 4294; Jones, Forbes, and Mueller, *Canad. J. Chem.*, 1957, **35**, 504.

[2] Mizushima, Shimanouchi, Miyazawa, Ichishima, Kuratani, Nakagawa, and Shindo, *J. Chem. Phys.*, 1953, **21**, 815.

[3] Nakagawa, Ichishima, Kuratani, Miyazawa, Shimanouchi, and Mizushima, *ibid.*, 1952, **20**, 1720.

more stable form in the solid state is that with the more polar conformation, and that this form is responsible for the higher of the two carbonyl frequencies of the liquid. This is in accord with the assignment which would be made on the basis of field effects. However, in chloroacetyl chloride both the carbonyl frequencies in the liquid state are reported at values which are lower than that of acetyl chloride and this also appeared to merit further investigation.

Experimental.—Samples were examined in a Grubb-Parsons S.3.A. double-beam spectrometer with a sodium chloride prism, or in a Grubb-Parsons G.S.2. double-beam grating instrument with a 2400 line/inch N.P.L. grating. The carbonyl frequencies of all the compounds measured with the prism spectrometer were checked against a standard run at the same time, and all frequencies are thought to be accurate within ± 1 cm.$^{-1}$. Acetone in carbon tetrachloride (1719 cm.$^{-1}$) or acetyl chloride vapour (1821 cm.$^{-1}$) were used as standards depending on the expected frequency range. Solutions were studied in 0·1 mm. cells while vapours, etc., were examined in 10 cm. cells. The acid chlorides studied were prepared by the reaction of the appropriate acid with benzoyl chloride. The product was then fractionally distilled and finally kept *in vacuo* to remove any alkyl halide which might have been formed by decomposition. Chloral was prepared by distilling chloral hydrate with concentrated sulphuric acid, dichloroacetaldehyde by depolymerisation of the commercially available material by vacuum-distillation, and monochloroacetaldehyde by repeated distillation of the semihydrate through anhydrous copper sulphate.

Results and Discussion.—The results are set out in the Table.

α-Halogenated aldehydes. Acetaldehyde itself absorbs at 1745 cm.$^{-1}$ in the vapour state, at 1730 cm.$^{-1}$ in CCl_4, and 1723 cm.$^{-1}$ in acetonitrile. The monochloro-derivative also shows only a single absorption band in the vapour (1752 cm.$^{-1}$), in CCl_4 (1742 cm.$^{-1}$), and in acetonitrile (1738 cm.$^{-1}$). Unfortunately this compound could not be studied in the crystalline state owing to the great ease of hydration. The appearance of only a single

Carbonyl frequencies (cm.$^{-1}$).

Compound	Vapour	In CCl_4	In MeCN
CH_3·COCl	1821	1806	1807
CH_2Cl·COCl	1835, 1798	1821, 1785	1817, 1786
Intensity ratio *	1·6	4·9	>8·5
$CHCl_2$·COCl	1823, 1790	1810, 1779	1805, 1783
Intensity ratio *	0·66	0·96	>2·0
CCl_3·COCl	1815	1803	1803
CH_3·CHO	1745	1730	1723
CH_2Cl·CHO	1752	1742	1738
$CHCl_2$·CHO	1761	1748	1744
CCl_3·CHO	1778	1768	1761

* The intensity ratio figures represent the ratio of the apparent max. extinction coeff. for the high- and the low-frequency CO bands respectively.

carbonyl band in solution is in marked contrast to the behaviour of chloroacetone and indicates that only a single rotational isomer is present. The frequencies in various solvents are all somewhat higher than for acetaldehyde but the shifts are much smaller than would have been expected for a conformation with an eclipsed chlorine–oxygen grouping. Trichloroacetaldehyde, for example, absorbs at 1778 cm.$^{-1}$ in the vapour state. Free rotation would lead to much broader bands than are found, so that it seems that the chlorine atom is predominately in a position such as (III), well away from the oxygen atom. This accords with Mizushima's hypothesis. The frequency shift must then be ascribed to residual inductive effects.

The results for dichloroacetaldehyde are also not as clear cut as those for α-chloroacetone. Only a single carbonyl band is shown in the vapour and in solution, again indicating the predominance of one rotational isomer. The frequencies are now intermediate between the values which might be expected for conformations which respectively

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have and have not eclipsed chlorine–oxygen atoms, and it is possible that some skew form such as (IV) is involved. No definite decision is possible from the data but it is significant that only one form is present and that this absorbs at a lower frequency than does the trichloro-product.

In trichloroacetaldehyde the carbonyl absorption is at 1778 cm.$^{-1}$ for the vapour and at 1768 cm.$^{-1}$ in CCl_4. In this form one chlorine must be eclipsed by the oxygen atom, or two chlorine atoms must lie in the vectorially equivalent conformation in which they are at 60° to the carbon–oxygen plane. The substantial frequency rise over the value for acetaldehyde is, therefore, to be expected on the basis of field effects.

The results for chlorinated aldehydes as a whole are not conclusive but the stabilisation of a single rotational isomer throughout, and the lower frequencies of the partially chlorinated members, provide some support for the view that the reduction in steric hindrance on passing from ketones to aldehydes leads to a stabilisation of conformations in which the chlorine is twisted away from the oxygen atom wherever possible.

α-Chloro-acid halides. Chloroacetyl chloride shows two carbonyl frequencies in the vapour, the liquid, and the solution state, and this has previously been established as due to rotational isomerism. Unlike the earlier workers we find that the higher of these two frequencies is appreciably above that of acetyl chloride, as would be expected from a field effect in the more polar *cis*-chlorine–oxygen conformation. The occurrence of two frequencies in the vapour state is in contrast to the situation with α-chloro-ketones which usually show only a single absorption under these conditions, corresponding to the less polar form. The presence of the second chlorine atom has therefore increased the stability of the *cis*-form, as would be expected from the steric and electrostatic repulsions between the chlorine atoms. As will be seen from the Table, dichloroacetyl chloride behaves similarly whilst trichloroacetyl chloride shows a single absorption as it can exist in only one form. These findings therefore further support Mizushima's hypotheses. However, their most interesting feature is the unusual behaviour of the carbonyl frequencies. The higher frequency band occurs at 1835 cm.$^{-1}$ in chloroacetyl chloride (vapour), representing a shift of 14 cm.$^{-1}$ from the frequency for acetyl chloride; for dichloroacetyl chloride this value falls to 1823 cm.$^{-1}$ which is within 2 cm.$^{-1}$ of that for the patent compound; for the trichloro-derivative, which must have a chlorine atom eclipsed with the oxygen, the frequency falls to 1815 cm.$^{-1}$, which is 6 cm.$^{-1}$ below that for acetyl chloride. As these higher frequency bands correspond to the more polar form this behaviour represents a marked difference from that of the α-chloro-ketones and similar materials.

The lower-frequency bands, corresponding to the less polar conformation, are also anomalous. In α-chloro-ketones these usually occur very close to the frequencies of the parent compounds. However, for chloroacetyl chloride this band is 23 cm.$^{-1}$ lower than that of acetyl chloride, and in dichloroacetyl chloride it falls even further.

The most logical explanation of these abnormalities is the possibility of field effects between two chlorine atoms, when one of them is at an angle of 120° to the oxygen, as well as the more normal effects between *cis*-chlorine–oxygen atoms. Although the two halogen atoms are further apart both are readily polarisable and some small interaction is to be expected. The high carbonyl frequencies of these compounds are determined primarily by the electronegativity of the element attached to the carbonyl group. The replacement of a methyl group of acetone by chlorine, for example, results in an upward shift of 81 cm.$^{-1}$ which is much greater than the shifts which arise from field effects. A field effect between the two chlorine atoms would lead to a reduction in the electronegativity of both from induced charges, and even a small change would therefore be expected to result in appreciable lowering of the carbonyl frequency. Effects of this type would be essentially additive and the suggestion is well supported by the self-consistency of the results from this point of view. The figures suggest that a chlorine atom which is eclipsed by the carbonyl-oxygen atom raises the frequency by about 14 cm.$^{-1}$, and that when it is at an angle of 120° the frequency is reduced by about the same amount. Starting with

the observation that acetyl chloride absorbs at 1821 cm.$^{-1}$ we can assess the remainder as follows:

	Form	ν (Calc.) (cm.$^{-1}$)	ν (Found) (cm.$^{-1}$)
CH_2Cl·COCl	Polar (1 *cis*-Cl)	1821 + 14 = 1835	1835
	Less polar (120° Cl)	1821 − 14 = 1807	1798
$CHCl_2$·COCl	Polar (1 *cis*-, 1 120° Cl)	1821 − 14 + 14 = 1821	1823
	Less polar (2 120° Cl)	1821 − 28 = 1793	1790
CCl_3·COCl	(1 *cis*-, 2 120° Cl)	1821 + 14 − 28 = 1807	1815

The postulate of additional field effects between the two chlorine atoms in suitable conformations therefore offers a reasonable explanation of these abnormal frequencies, and a compound such as chloroacetyl chloride provides an interesting example of a molecule in which different field effects occur in the two rotational isomers and operate there in opposite directions.

E.R.D.E., Ministry of Supply,
Waltham Abbey, Essex.

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699. *Immunopolysaccharides. Part X.* The Structure of the Immunologically Specific Polysaccharide of* Pneumococcus *Type XIV.*

By S. A. Barker, M. Heidelberger, M. Stacey, and D. J. Tipper.

Pneumococcus Type XIV polysaccharide has been shown to contain D-glucose, D-galactose, and 2-acetamido-2-deoxy-D-glucose residues. Partial acidic hydrolysis of the polysaccharide gave, *inter alia*, two disaccharides which were assigned the probable structures 4-*O*-β-D-glucosyl-2-acetamido-2-deoxy-D-glucose and 3-*O*-β-(2-acetamido-2-deoxy)-D-glucosyl-D-galactose. Hydrolysis of the methylated polysaccharide gave 3-*O*-methyl-D-glucosamine (1 part) and neutral sugars (2 parts) consisting of 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose <4%, 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose and 2 : 3 : 6-tri-*O*-methyl-D-glucose 69%, 2 : 4 : 6-tri-*O*-methyl-D-galactose 23%, and di-*O*-methylhexose 4%.

From a chemical investigation of *Pneumococcus* Type XIV polysaccharide, Goebel, Beeson, and Hoagland [1] concluded that it was a polymer consisting of units of 2-acetamido-2-deoxy-D-glucose and D-galactose in the ratio 1 : 3. Preliminary studies by three of us [2] indicated that the substance contained D-glucose as an additional constituent which was liberated under more drastic conditions of acid hydrolysis (2N-sulphuric acid at 100° for 4 hr.) than those used by Goebel, Beeson, and Hoagland [1] (N-acid at 100° for 2·5 hr.). Recent immunological studies [3-6] on the cross-reactivity of antiserum to Type XIV *Pneumococcus* made it appear certain that *Pneumococcus* Type XIV polysaccharide would contain non-reducing end groups of D-galactose together with D-galactose residues linked β-1 : 3 or β-1 : 6, or involved in β-1 : 3 : 6-branch points. The present investigation was undertaken to test these predictions by purely chemical methods and to elucidate the principal structural features of *Pneumococcus* Type XIV polysaccharide.

Purified Type XIV polysaccharide on acid hydrolysis afforded galactose, glucose, and glucosamine together with glutamic acid. Similar hydrolysis of a sample of the original Type XIV polysaccharide studied by Goebel and his co-workers [1] gave the same three sugars but no glutamic acid. The absence of glutamic acid can probably be ascribed to the use of nitrous acid in the purification procedure of these workers.[1] Moreover, the

* Part IX, *J.*, 1958, 1895.

[1] Goebel, Beeson, and Hoagland, *J. Biol. Chem.*, 1939, **129**, 455.
[2] Heidelberger, Barker, and Stacey, *Science*, 1954, **120**, 781.
[3] Heidelberger, Dische, Neely, and Wolfrom, *J. Amer. Chem. Soc.*, 1955, **77**, 3511.
[4] Heidelberger, *ibid.*, p. 4308.
[5] Heidelberger, Barker, and Björklund, *ibid.*, 1958, **80**, 113.
[6] Rebers, Barker, Heidelberger, Dische, and Evans, *ibid.*, p. 1135.

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substance (probably a peptide) which gave glutamic acid on hydrolysis could be removed from purified Type XIV polysaccharide by prolonged dialysis or by precipitation with Type XIV antiserum which had previously been absorbed with the somatic C-polysaccharide of *Pneumococcus*, and recovery of the type-specific polysaccharide from the washed precipitate. Finally, dialysed purified Type XIV polysaccharide moved as a single homogeneous component, except for a small nucleic acid impurity, when separated in borate buffer pH 9·2 in a Tiselius electrophoresis apparatus.

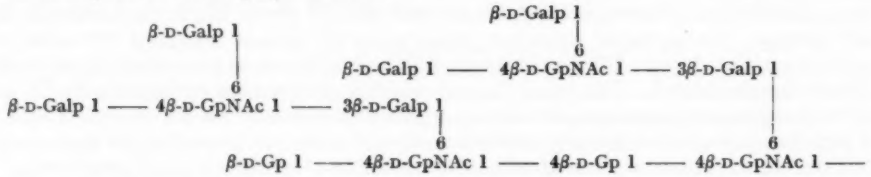
Type XIV polysaccharide was submitted to partial acidic hydrolysis and after *N*-acetylation the mixture was fractionated on a charcoal–Celite column.[7] The monosaccharide components were characterised as crystalline α-D-galactopyranose and 2-acetamido-2-deoxy-α-D-glucose. The glucose present was isolated as its crystalline β-penta-acetate and as *N*-*p*-nitrophenyl-β-D-glucopyranosylamine.

Two disaccharides (III and IV) constituted the major part of the disaccharide fractions. Two other disaccharides (I and II) detected occurred in insufficient amounts for characterisation. On acid hydrolysis, disaccharide III gave galactose and glucosamine, while disaccharide IV gave glucose and glucosamine. Analysis of the acid hydrolysate of the disaccharide alcohol, obtained from III by reduction with sodium borohydride, showed that the only reducing sugar present was glucosamine. Similar analysis of disaccharide IV alcohol hydrolysate revealed glucose as the only reducing sugar. This indicated that III was a 2-acetamido-2-deoxyglucosylgalactose and that IV was a glucosyl-2-acetamido-2-deoxyglucose. On periodate oxidation, disaccharide IV alcohol consumed 2·8 moles of periodate and produced 1·35 moles of formic acid and 0·85 mole of formaldehyde per mole of disaccharide alcohol. This was in accord with the formulation of disaccharide IV as 4-*O*-D-glucopyranosyl-2-acetamido-2-deoxy-D-glucose (theoretical for its alcohol, 3 mols. of periodate consumed and 1 mol. of formic acid and 1 mol. of formaldehyde produced). This structure is also in agreement with its low mobility (M_G 0·16) on paper ionophoresis [8] in borate buffer, pH 10. The large amount of periodate consumed (6·6 mols.) by disaccharide III alcohol and the large amounts of formic acid (4·1 mols.) and formaldehyde (2·4 mols.) produced suggested that over-oxidation was occurring, possibly owing to production of a malondialdehyde derivative from a 1 : 3- or 1 : 4-linked disaccharide alcohol. The alkali-lability of disaccharide III and its high mobility in borate buffer of pH 10 (M_G 0·57) were in favour of the structure 3-*O*-(2-acetamido-2-deoxy)-D-glucosyl-D-galactose. The structures assigned to both these disaccharides receive further confirmation from the study of methylated Type XIV polysaccharide reported below.

Exhaustive methylation of Type XIV polysaccharide with sodium and methyl iodide in liquid ammonia [9] afforded a methyl ether (I), OMe 37·1% (a methylated polymer consisting of two hexose units for every *N*-acetylglucosamine unit requires OMe, 38·8%). Another sample (II) obtained by methylation with sodium hydroxide and methyl sulphate had OMe, 34·4%. Methanolysis and hydrolysis of II followed by passage down a column of Dowex 50(H^+) gave a neutral methyl-sugar fraction and basic methyl-hexosamine fraction. The latter consisted of a single component which was identical with 3-*O*-methyl-D-glucosamine both in its behaviour when chromatographed and in the products of oxidation by ninhydrin.[10] Further confirmation was obtained by periodate oxidation of the alcohol produced by reduction with sodium borohydride: this consumed 1·8 mols. of periodate and produced 0·56 mol. of formic acid and 1·1 mol. of formaldehyde compared with the theoretical figures of 2, 1, and 1 respectively for 2-acetamido-2-deoxy-3-*O*-methyl-D-glucitol. The neutral methyl-sugars obtained were fractionated on a cellulose column. One of these fractions on treatment with aniline in ethanol afforded 2 : 3 : 4 : 6-tetra-*O*-methyl-*N*-phenyl-D-galactosylamine. Owing to the small amounts available,

[7] Whistler and Durso, *J. Amer. Chem. Soc.*, 1950, **72**, 677.
[8] Foster, *J.*, 1953, 982.
[9] Freudenberg and Boppel, *Ber.*, 1938, **71**, 2505.
[10] Gardell, Heijenskjold, and Rochnorlund, *Acta Chem. Scand.*, 1950, **4**, 970.

and the fact that most of the fractions obtained were mixtures, a further batch of neutral sugars was isolated by a similar procedure from the product (I) of sodium–methyl iodide methylation. Quantitative analysis [11] of the mixture of neutral methyl-sugars showed that it consisted of: 2 : 3 : 4 : 6-tetra-*O*-methylglucose, <4%; 2 : 3 : 4 : 6-tetra-*O*-methylgalactose and 2 : 3 : 6-tri-*O*-methylglucose, 69%; 2 : 4 : 6-tri-*O*-methylgalactose, 23%; and di-*O*-methylhexose, 4%. Three of these were isolated as the following crystalline derivatives: 2 : 3 : 4 : 6-tetra-*O*-methyl-*N*-phenyl-D-galactosylamine, 2 : 3 : 6-tri-*O*-methyl-β-D-glucose 1 : 4-di-*O*-*p*-nitrobenzoate, and 2 : 4 : 6-tri-*O*-methyl-*N*-phenyl-D-galactosylamine. From the weights of methyl-sugars isolated and the quantitative estimation it was concluded that for every six sugar residues, two were non-reducing end groups of D-galactose, one was a D-galactose residue linked through positions 1 and 3, one was a D-glucose residue linked through positions 1 and 4, and two were 1 : 4 : 6-linked 2-acetamido-2-deoxy-D-glucose residues engaged in branching. A small number of glucose residues (<1 in 25) were non-reducing end groups and the di-*O*-methylhexose fraction could be attributed to either incomplete methylation or to hexose residues involved in branching. In the arrangement shown below all the linkages are assigned the β-configuration on the basis of (*a*) the low optical rotation of both the polysaccharide itself (+9·4°) [1] and its methyl ether (+18°) and (*b*) the absence of Type 2a absorption [12] in the infrared spectrum of the polysaccharide.



Type XIV polysaccharide was submitted to periodate oxidation initially at room temperature and later at 25°. For every six sugar residues of the type postulated above it consumed 4·9 mols. of periodate and produced 2·05 mols. of formic acid compared with the theoretical values of 5 and 2 respectively. The periodate-oxidised polysaccharide precipitated less than one-half of the antibody in a Type XIV antipneumococcal horse serum.[5] Acidic hydrolysis of the periodate-oxidised polysaccharide yielded galactose and glucosamine but no glucose. Partial hydrolysis, as would be predicted, yielded *inter alia* disaccharide III but no disaccharide IV.

Experimental

Purification of Pneumococcus *Type XIV Polysaccharide.*—The crude polysaccharide was kindly supplied by E. R. Squibb and Sons Ltd., of New Brunswick, New Jersey. A typical purification procedure (Sevag [13]) involved removal of the protein present in the crude polysaccharide (4 g.) by shaking its aqueous solution (300 ml.) several times with chloroform–pentyl alcohol (9 : 1) (4 × 30 ml.). The aqueous phase was then passed through a column of Nalcite (H^+ form) which was further washed with water (50 ml.). This operation was performed in the refrigerator. The polysaccharide in the eluate was precipitated with propan-2-ol (equal volume) after addition of 5% lithium chloride (10 ml.). The precipitate was taken up in water (235 ml.), and the solution centrifuged and again precipitated with propan-2-ol (220 ml.), washed with alcohol and acetone, and dried (yield, 2·2 g.).

Part (10 mg.) of the purified polysaccharide was hydrolysed with 2N-sulphuric acid (1 ml.) at 100° for 4 hr. and the neutralised hydrolysate separated by paper ionophoresis [8] in borate buffer (pH 10). Spraying with aniline hydrogen phthalate [15] revealed the presence of

[11] Hirst, Hough, and Jones, *J.*, 1949, 928.
[12] Barker, Bourne, Stacey, and Whiffen, *J.*, 1954, 171.
[13] Sevag, *Biochem. Z.*, 1934, **273**, 419.
[14] Partridge, *Nature*, 1949, **164**, 443.
[15] Roseman and Ludowieg, *J. Amer. Chem. Soc.*, 1954, **76**, 301.

components having mobilities identical with those of glucose, galactose, and glucosamine together with an unidentified component. Paper ionophoresis in citrate–phosphate buffer of pH 6·2 and spraying with ninhydrin showed a component with the mobility of glucosamine and showed that the unidentified component had a mobility expected of a disaccharide containing one hexosamine residue. In addition an acidic component with the mobility of glutamic acid was detected.

Anti-type XIV *Pneumococcus* serum (15 ml.) was incubated with some of the purified polysaccharide (2 mg.) at 0° for 24 hr. and the specific precipitate obtained washed thoroughly with 0·9% saline solution. The specific polysaccharide was extracted from the precipitate with 5% trichloroacetic acid [3] and then hydrolysed as above. Paper-ionophoretic analysis (as above) showed the presence of all the components previously detected. However, precipitation of the purified polysaccharide (3 mg.) with C-absorbed Type XIV antiserum (11 ml.) and recovery from the washed precipitate gave a glutamic acid-free polysaccharide. A similar glutamic acid-free polysaccharide was obtained on prolonged dialysis of the purified polysaccharide against saline solution.

Homogeneity of Type XIV Pneumococcus *Polysaccharide*.—Dialysed purified polysaccharide (130 mg.) in borate buffer (pH 9·2; 15 ml.) was dialysed against more borate buffer (pH 9·2; 4 l.) for 3 days. The centrifuged polysaccharide solution and isotonic borate buffer were placed in the medium cell of a Tiselius electrophoresis apparatus, and the current (5·5 mA) was applied. Except for a small fast-moving impurity, the Type XIV polysaccharide moved as a single homogeneous component for 2 hr. The fast-moving impurity was trapped and was found to be ribonucleic acid from (*a*) its ultraviolet absorption peak at 259 mμ and (*b*) the production of ribose on acid hydrolysis.

Infrared Spectrum of Type XIV Pneumococcus *Polysaccharide*.—The infrared spectrum of the polysaccharide was measured as a mull in liquid paraffin with a single-beam Grubb–Parsons spectrometer. It showed absorption peaks at 1642 and 1551 cm.$^{-1}$ (C=O stretching and N–H bending of an *N*-acetyl group). In the region 720—1000 cm.$^{-1}$ the absence of absorption [12] around 840 cm.$^{-1}$ (type 2a) and the presence of a peak at 890 cm.$^{-1}$ (type 2b) indicated that the majority of the linkages in the polysaccharide were of the β-type.

Partial Acidic Hydrolysis of the Polysaccharide.—The polysaccharide (4·8 g.) was hydrolysed with N-hydrochloric acid (150 ml.) at 100° for 2·5 hr. After neutralisation with silver carbonate the solution was concentrated by freeze-drying (to 100 ml.) and the hexosamine-containing saccharides were *N*-acetylated by Roseman and Ludovieg's method [15] with acetic anhydride (2 ml.) and Amberlite IRA-400 (CO_3^{2-}) (15 ml.) in 10% aqueous methanol. Any unacetylated hexosamine-containing saccharides were removed by passage down a column of Amberlite IR-120(H^+). The resulting mixture of saccharides was fractionated [7] on a charcoal–Celite column (*l* 34 cm.; diam. 6 cm.). Gradient elution (0 ⟶ 25% aqueous ethanol; 15 l.) gave fraction A (1·275 g.) (glucose, galactose, and traces of ribose), B (0·344 g.) (2-acetamido-2-deoxyglucose and traces of ribose), C (0·057 g.) (a mixture of disaccharides I and II), D (0·156 g.) (disaccharide III), E (0·202 g.) (disaccharide IV with small amounts of disaccharide III and a trisaccharide), F (0·263 g.) (trisaccharides and higher saccharides).

Characterisation of monosaccharides. Crystallisation of A from methanol gave α-D-galactopyranose (0·835 g.), m. p. and mixed m. p. 164—165°, $[\alpha]_D^{17}$ +126° (3 min.) ⟶ +80·8° equil. (*c* 0·39 in H_2O) (Found: C, 40·0; H, 6·6. Calc. for $C_6H_{12}O_6$: C, 40·0; H, 6·7%). The mother-liquors were separated on sheets of Whatman No. 3 paper irrigated with the organic phase of butanol–ethanol–water–ammonia (40 : 10 : 49 : 1). Part (0·055 g.) of the glucose component eluted from the paper (0·180 g.) was refluxed for 15 min. with *p*-nitroaniline (12 mg.) in acidified methanol (5 ml.) [16] to give *N*-*p*-nitrophenyl-β-D-glucopyranosylamine (34 mg.), m. p. and mixed m. p. 182—183°, $[\alpha]_D^{17}$ −193° (5 min.) ⟶ −204° equil. (*c* 1·22 in dry pyridine) (Found: C, 45·5; H, 5·6. Calc. for $C_{12}H_{16}O_7N_2,H_2O$: C, 45·3; H, 5·7%). The glucose component was further characterised as β-D-glucose penta-acetate, m. p. and mixed m. p. 134—134·5°.

Crystallisation of B from alcohol–ether gave 2-acetamido-2-deoxy-α-D-glucose (0·135 g.), m. p. and mixed m. p. 195—196°, $[\alpha]_D^{17}$ +56° (6 min.) ⟶ +42° equil. (*c* 0·32 in H_2O) (Found: C, 43·4; H, 6·9; N, 6·0. Calc. for $C_8H_{15}O_6N$: C, 43·5; H, 6·8; N, 6·3%).

Characterisation of disaccharides. Chromatographically pure disaccharides III and IV, obtained from fractions D and E, showed M_G 0·57 and 0·16 respectively when separated by paper ionophoresis [8] in borate buffer of pH 10.

[16] Weygand, Perkow, and Kuhner, *Chem. Ber.*, 1951, **84**, 594.

Disaccharides III and IV had $R_{Glucose}$ 0·40 and 0·47 respectively in butan-1-ol–ethanol–water–ammonia (40 : 10 : 49 : 1), $R_{Glucose}$ 0·36 and 0·39 in butan-1-ol–acetic acid–water (40 : 10 : 50), and $R_{Glucose}$ 0·68 and 0·82 in pentyl alcohol–pyridine–water (1 : 1 : 1). Both disaccharides were detected by aniline hydrogen phthalate (III, brown; IV, orange-brown) and the Elson–Morgan reagent.

Disaccharides III and IV (3 mg.) were hydrolysed separately with 2N-sulphuric acid (0·5 ml.) for 7·5 hr. at 100°. Paper-ionophoretic analysis of disaccharide III hydrolysate showed galactose and glucosamine while disaccharide IV hydrolysate contained glucose and glucosamine. Portions of III and IV (30 mg.) in water (3 ml.) were reduced separately with sodium borohydride (40 mg.) in water (0·5 ml.) for 5 hr. at room temperature and part (1 mg.) of the de-ionised product from both was submitted to hydrolysis with 2N-sulphuric acid (0·5 ml.) for 5 hr. at 100°. Paper-ionophoretic analysis of the reducing sugars present in disaccharide III alcohol hydrolysate showed glucosamine only and in disaccharide IV alcohol hydrolysate showed glucose only.

Disaccharide III alcohol (8·6 mg.) and disaccharide IV alcohol (12·1 mg.) were each oxidised separately at 17° with 0·02M-sodium periodate (50 ml.). The periodate consumption expressed in moles per mole of disaccharide alcohol after 26 hr. was: III, 6·6 and IV, 2·8. After 26 hr., 4·1 moles of formic acid and 2·4 moles of formaldehyde had been produced per mole of disaccharide III alcohol, and 1·35 moles of formic acid and 0·85 mole of formaldehyde per mole of disaccharide IV alcohol.

Methylation of the Polysaccharide.—The polysaccharide (3·15 g.) was treated with sodium and methyl iodide in liquid ammonia at −55° by a modification of the methods employed by Freudenberg and Boppel [9] and by Hodge, Karjala, and Hilbert.[17] After four additions of the methylating reagents (reaction times: sodium, 4 hr.; methyl iodide, 0·5 hr.) had been made, the ammonia was allowed to evaporate with the exclusion of moisture, the last traces being removed at 75°/15 mm. After dialysis and freeze-drying, the methylation procedure was repeated. The product was suspended in chloroform and centrifuged and the residue (0·23 g.; OMe, 5·6%) discarded. Addition of light petroleum (b. p. 40—60°) to the supernatant liquid precipitated methylated polysaccharide (1·25 g.; OMe, 32%) and a further fraction (0·68 g.; OMe, 35%) was recovered from the mother-liquors. These fractions were recombined and the methylation procedure repeated. That portion of the product soluble in chloroform–light petroleum (1·79 g.; methylated polysaccharide I) had OMe, 37·1%, and $[\alpha]_D^{12}$ +18° (*c* 0·61 in $CHCl_3$).

A second sample of the polysaccharide (1·9 g.) was methylated four times with methyl sulphate and sodium hydroxide,[18] and the crude product (1·64 g.) fractionated with chloroform–light petroleum to methylated polysaccharide II (0·517 g.; OMe, 34·4%) and another fraction (0·873 g.; OMe, 28·0%).

Identification of the Methyl-sugars obtained from the Methylated Polysaccharide.—(a) *3-O-Methyl-D-glucosamine.* Methylated polysaccharide II (0·5 g.) was refluxed with 5% methanolic hydrogen chloride (50 ml.) for 9 hr. After neutralisation with silver carbonate and removal of methanol the resulting methyl glycosides were hydrolysed with aqueous 3·8% hydrochloric acid (50 ml.) at 100° for 7·5 hr. After neutralisation, the product was passed down a column of Dowex 50 (H^+) and the neutral sugars (0·34 g.) were eluted with water. Washing with 3·8% hydrochloric acid eluted the amino-sugar fraction which consisted of a single component having paper chromatographic and staining properties identical with those of 3-*O*-methyl-D-glucosamine. Portions (5 mg.) both of the amino-sugar fraction and of authentic 3-*O*-methyl-D-glucosamine were oxidised separately with ninhydrin. Paper-chromatographic separation showed that they gave identical products, one of which had the properties reported for 2-*O*-methylarabinose [R_F 0·40 in butanol–ethanol–water (40 : 10 : 50); Lederer and Lederer [19] quote R_F 0·38]. Paper ionophoresis in borate buffer of pH 10 also showed identical products.

A further portion (20 mg.) of the amino-sugar fraction was treated with acetic anhydride (0·5 ml.) and Amberlite IRA-400 (CO_3^{2-}; 25 ml.) in aqueous 10% methanol (25 ml.) at 0° for 1·5 hr. After further purification by passage down an Amberlite IR-120(H^+) column, the product was reduced with sodium borohydride (100 mg.). The resulting 2-acetamido-2-deoxy-3-*O*-methyl-D-glucitol (14 mg.) was oxidised with 0·04M-sodium periodate (12 ml.) at 17°.

[17] Hodge, Karjala, and Hilbert, *J. Amer. Chem. Soc.*, 1951, **73**, 3312.
[18] Haworth, *J.*, 1915, **107**, 8.
[19] Lederer and Lederer, "Chromatography," Elsevier Ltd., Amsterdam, p. 164.

After 24 hr., 1·8 moles of periodate had been consumed and 0·56 mole of formic acid and 1·1 mole of formaldehyde had been produced per mole of 2-acetamido-2-deoxy-3-*O*-methyl-D-glucitol.

(b) *Neutral sugars.* The neutral sugars (0·27 g.) were fractionated on a cellulose column washed with butanol–ethanol–water–ammonia (40 : 10 : 49 : 1). Paper-chromatographic analysis of the fractions indicated that I (56 mg.) contained 2 : 3 : 4 : 6-tetra-*O*-methylgalactose and 2 : 3 : 6-tri-*O*-methylglucose, II (99 mg.) contained the same two sugars together with 2 : 4 : 6-tri-*O*-methylgalactose, III (62 mg.) was mainly 2 : 4 : 6-tri-*O*-methylgalactose, and IV (45 mg.) was a mixture of di- and mono-methyl-sugars. Treatment of I with aniline in ethanol gave 2 : 3 : 4 : 6-tetra-*O*-methyl-*N*-phenyl-D-galactosylamine (24 mg.), m. p. and mixed m. p. 192° (Found: C, 61·7; H, 8·0; N, 4·6. Calc. for $C_{16}H_{25}O_5N$: C, 62·2; H, 8·0; N, 4·4%).

More neutral sugars were obtained as follows: methylated polysaccharide I (1·6 g.) was refluxed with 5% methanolic hydrogen chloride (170 ml.) to constant optical rotation. The resulting methyl glycosides were hydrolysed with N-hydrochloric acid (170 ml.) for 10 hr. at 100°, and the solution freed from ions and concentrated to a syrup (1·59 g.). The methyl sugars were then passed down a column of Amberlite IR-120 (H^+) (200 ml.). The neutral sugars (1·07 g.) were not absorbed and washing the column with 2·5N-hydrochloric acid (500 ml.) eluted the basic methyl sugar fraction (0·52 g.). A portion (5—7 mg.) of the neutral sugar fraction was analysed quantitatively by paper chromatographic separation in butanol–ethanol–water–ammonia (40 : 10 : 49 : 1), elution from the paper and estimation of the components by hypoiodite oxidation according to the method of Hirst, Hough, and Jones.[11] The percentage molecular composition was: 2 : 3 : 4 : 6-tetra-*O*-methylglucose, <4%; 2 : 3 : 4 : 6-tetra-*O*-methylgalactose and 2 : 3 : 6-tri-*O*-methylglucose, 69%; 2 : 4 : 6-tri-*O*-methylgalactose, 23%; and di-*O*-methylhexose, 4%. The remainder (1·06 g.) of the neutral sugars were fractionated on a cellulose column as above, to give A (78 mg.) (mainly 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose), B (564 mg.) (2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose and 2 : 3 : 6-tri-*O*-methyl-D-glucose), C (107 mg.) (same sugars as B together with some 2 : 4 : 6-tri-*O*-methyl-D-galactose), D (197 mg.) (2 : 4 : 6-tri-*O*-methyl-D-galactose), and E (43 mg.) (mainly a di-*O*-methylhexose).

Fraction B (161 mg.) was refluxed with aniline (0·16 ml.) in ethanol (1·5 ml.) for 3 hr. Recrystallisation of the product (51 mg.) from ethanol gave 2 : 3 : 4 : 6-tetra-*O*-methyl-*N*-phenyl-D-galactosylamine, m. p. and mixed m. p. 193—194°, $[\alpha]_D^{17}$ +40° (equil.) (*c* 0·3 in EtOH). The concentrated mother-liquors from this anilide formation were heated with Amberlite IR-120(H^+) (10 g.) in water (30 ml.) for 3 hr. at 85°. The syrup (77 mg.) obtained on concentration was heated with *p*-nitrobenzoyl chloride (180 mg.) in dry pyridine (5 ml.) for 0·5 hr. at *ca.* 70°. Recrystallisation of the product from methanol gave 2 : 3 : 6-tri-*O*-methyl-β-D-glucose 1 : 4-di-*p*-nitrobenzoate, m. p. and mixed m. p. 188—189°, $[\alpha]_D^{17}$ −31° (*c* 0·4 in MeOH) (Calc. for $C_{33}H_{34}O_{12}N_2$: N, 5·4. Found: N, 5·3%). Rebers and Smith [20] give m. p. 189—190° and $[\alpha]_D$ −33° in chloroform. Fraction B (343 mg.) was partitioned 28 times between equal volumes of chloroform and water. The chloroform phase contained mainly 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose (210 mg.), and the aqueous phase contained mainly 2 : 3 : 6-tri-*O*-methyl-D-glucose (110 mg.). Treatment of some (17·6 mg.) of the latter with 4% methanolic hydrogen chloride at room temperature caused $[\alpha]_D^{17}$ +50° (4 min.) to become −18° (120 min.) (*c*, 0·22) and complete loss of staining power with aniline hydrogen phthalate.

Fraction D (112 mg.) was refluxed with aniline (0·11 ml.) in ethanol (1 ml.) for 3 hr. Recrystallisation of the product from ethanol gave 2 : 4 : 6-tri-*O*-methyl-*N*-phenyl-D-galactosylamine (46 mg.), m. p. and mixed m. p. 174—176°, $[\alpha]_D^{17}$ −44·1° equil. (*c* 1·12 in EtOH) (Found: C, 60·7; H, 8·0; N, 4·7. Calc. for $C_{15}H_{23}O_5N$: C, 60·6; H, 7·8; N, 4·7%).

Periodate Oxidation of Type XIV Polysaccharide.—The polysaccharide (231 mg.) was oxidised with 0·016M-sodium periodate in the dark for 4 days at room temperature, then for 19 days at 25°. The number of moles of periodate consumed per 1054 gm. of polysaccharide was: 0·75 day, 3·15; 4 days, 3·48; 6 days, 3·9; 8 days, 4·3; 11 days, 4·5; 16 days, 4·7; 23 days, 4·9. The corresponding number of moles of formic acid produced was: 0·75 day, 1·25; 4 days, 1·5; 6 days, 1·7; 8 days, 1·8; 23 days, 2·05.

A portion (37 mg.) of the periodate-oxidised polysaccharide recovered (198 mg.) was hydrolysed with 2·8N-hydrochloric acid (5 ml.) for 7 hr. at 100°. After neutralisation with silver carbonate the hydrolysate was *N*-acetylated.[7] Paper-chromatographic analysis of the resulting mixture showed 2-acetamido-2-deoxyglucose and galactose but no glucose. Using

[20] Rebers and Smith, *J. Amer. Chem. Soc.*, 1954, **76**, 6097.

less drastic conditions of hydrolysis (2N-hydrochloric acid for 6 hr. at 100°) we detected the same sugars together with a disaccharide. The latter gave galactose and glucosamine on further acidic hydrolysis and had a mobility identical with that of disaccharide III on ionophoresis in borate buffer of pH 10. No disaccharide IV was detected.

The authors are greatly indebted to Dr. Walter F. Goebel for a sample of Type XIV *Pneumococcus* polysaccharide and to Mr. Arnold Powell for technical assistance. One of them (D. J. T.) thanks the University of Birmingham for the award of a Scholarship.

CHEMISTRY DEPT., THE UNIVERSITY, BIRMINGHAM, 15.
INSTITUTE OF MICROBIOLOGY, RUTGERS UNIVERSITY,
NEW BRUNSWICK, N.J., U.S.A.

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700. *Organic Peroxides. Part VIII.* The Stereochemistry and Mechanism of the Preparation and Reduction of* 1-*Methyl*-1-*phenylpropyl Hydroperoxide.*

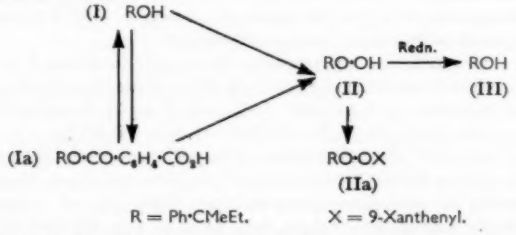
By ALWYN G. DAVIES.

Treatment of optically active 2-phenylbutan-2-ol or its hydrogen phthalate with hydrogen peroxide gives the active hydroperoxide, which can be reduced back to the active alcohol. It is concluded that the reductions proceed with complete retention of configuration in the 1-methyl-1-phenylpropyl group, and therefore that the hydroperoxide is formed from the alcohol and from the hydrogen phthalate with predominating retention of configuration, by an S_Ni mechanism.

IN Part VI [1] we reported a stereochemical study of the formation and reduction of 1-phenylethyl hydroperoxide. The availability of optically active 2-phenylbutan-2-ol and its hydrogen phthalate [2] has enabled us to carry out a similar study of 1-methyl-1-phenylpropyl hydroperoxide.

RESULTS

We have shown previously [3] that hydrogen peroxide reacts with the alcohol (I) under acid conditions, and with the sodium salt of the hydrogen phthalate (Ia) giving the hydroperoxide (II); treatment of the hydroperoxide with xanthhydrol gives the 9-xanthenyl derivative (IIa). These reactions have now been repeated with the optically active compounds; the rotatory powers of the reactants and products are shown in the first two columns respectively of Tables 3, 4, and 2. Under neutral conditions the active alcohol was partially converted into the hydroperoxide which was isolated as its 9-xanthenyl derivative [3] (IIa); data on this reaction are included in Table 3.



Experiments with the [^{18}O]alcohol and hydrogen phthalate showed that the reaction of both with hydrogen peroxide proceeds by alkyl–oxygen fission (cf. Part V [4]).

* Part VII, *J.*, 1956, 4669.

[1] Davies and Feld, *J.*, 1956, 665.
[2] Davies, Kenyon, and Salamé, *J.*, 1957, 3148.
[3] Davies, Foster, and White, *J.*, 1954, 2200.
[4] Bassey, Bunton, Davies, Lewis, and Llewellyn, *J.*, 1955, 2471.

The optically active hydroperoxide (II) was then reduced back to the alcohol (III) with sodium sulphite, hydrogen and platinum, zinc and acetic acid, and lithium aluminium hydride; the results are recorded in Table 1.

The Steric Course of the Reduction of the Hydroperoxide [(II) ⟶ (III)].—The sensibly constant ratio of α_{III}/α_{II} (Mean, +0·37; Table 1) shows that the reductions of the hydroperoxide with the four reagents must all have the same stereochemical result. This implies that these reductions, like those of 1-phenylethyl hydroperoxide,[1] all proceed with configurational retention. Therefore 2-phenylbutan-2-ol and 1-methyl-1-phenylpropyl hydroperoxide of the same sign of rotation have corresponding configurations (cf. the 1-phenylethyl [1] and 1-methylhexyl [5] compounds), and if we assume that the maximum rotatory power of the alcohol is $\alpha_D = 18{\cdot}1°$,[2,6] the optically pure hydroperoxide has α_D = *ca.* 49°.

TABLE 1. *Reduction of hydroperoxide* (II) *to alcohol* (III).

α_{II}	α_{III}	Reagent	α_{III}/α_{II}
+0·60°	+0·21°	Na_2SO_3	+0·35
+4·05	+1·55	Zn–HOAc	+0·38
+4·05	+1·54	$LiAlH_4$	+0·38
+4·05	+1·55	H_2–Pt	+0·38
		Mean:	+0·37

TABLE 2. *Conversion of hydroperoxide into xanthenyl derivative* (IIa).

α_{II}	α_{IIa}	α_{II}/α_{IIa}
+4·05°	+3·46°	+1·17
+1·81	+1·3	+1·4
	Mean:	+1·3

TABLE 3. *Conversion of alcohol into hydroperoxide*

	α_I	α_{II}	$[\alpha]_{IIa}$	α_{III}/α_I
Acid ...	+6·00°	+0·61°	—	+3·8% [a]
	+6·24	+0·26	—	+1·5% [a]
Neutral	−11·62	—	−1·07°	+4·4% [b]

[a] Derived from $\alpha_{III}/\alpha_{II} \times \alpha_{II}/\alpha_I$.
[b] Derived from $[\alpha]_{IIa}/\alpha_I \times \alpha_{II}/[\alpha]_{IIa} \times \alpha_{III}/\alpha_{II}$. Values for α_{III}/α_{II} and $\alpha_{II}/[\alpha]_{IIa}$ are taken from Tables 1 and 2.

TABLE 4. *Conversion of hydrogen phthalate* (Ia) *into hydroperoxide* (II)

$[\alpha]_{Ia}$	α_{II}	α_{III}/α_I
−43°	+4·05°	+9·1% [c]
−15	+1·81	+11·6%

[c] Derived from $\alpha_{II}/[\alpha]_{Ia} \times [\alpha]_{Ia}/\alpha_I \times \alpha_{III}/\alpha_{II}$. The value for α_{III}/α_{II} is taken from Table 1. $[\alpha]_{Ia}/\alpha_I = -2{\cdot}6$ (see below).

The Steric Course of the Formation of the Hydroperoxide from the Alcohol [(I) ⟶ (II)] *and the Hydrogen Phthalate* [(Ia) ⟶ (II)].—We accept therefore that the hydroperoxide (II) is reduced to the alcohol (III) with 100% retention of configuration, such that $\alpha_{III}/\alpha_{II} = +0{\cdot}37$. The value of $\alpha_{III}/\alpha_{II} \times \alpha_{II}/\alpha_I$ recorded for the reaction of the alcohol under acid conditions, in Table 3, therefore gives a measure of the configurational result of the reaction (I) ⟶ (II): under acid conditions the hydroperoxide is formed from the alcohol with at least +3·8 to +1·5% retention of purity of configuration. These values, and those derived below, are minimal because no allowance has been made for any racemisation of the reactant or product previous or subsequent to reaction, respectively.

It is safe to assume that the hydroperoxide (II) is converted into the 9-xanthenyl derivative (IIa) with complete retention of configuration in the 1-methyl-1-phenylpropyl group.[1,3] The value of $\alpha_{II}/[\alpha]_{IIa}$ in Table 2 therefore represents in sign and magnitude the ratio of the rotatory powers of (II) and (IIa) of corresponding configuration. The expression $[\alpha]_{IIa}/\alpha_I \times \alpha_{II}/[\alpha]_{IIa} \times \alpha_{III}/\alpha_{II}$ (Table 3) therefore represents the configurational result of the reaction (I) ⟶ (II): under neutral conditions the hydroperoxide is formed from the alcohol with +4·4% retention of purity of configuration.

To derive the corresponding result for the formation of the hydroperoxide from the hydrogen phthalate [(Ia) ⟶ (II)] we need to know the relation in sign and magnitude between the alcohol and the hydrogen phthalate, $[\alpha]_{Ia}/\alpha_I$. Zeiss [6] showed that the hydrogen phthalate ($[\alpha]_D$ +11·8°) gave, with complete retention, the alcohol (α_D −4·53°), whence $[\alpha]_{Ia}/\alpha_I = -2{\cdot}60$. Similarly Davies, Kenyon, and Salamé [2] found that the hydrogen phthalate ($[\alpha]_D^{20}$ +48·3°) corresponds to the alcohol ($\alpha_D^{21{\cdot}5}$ −18·4°), whence $[\alpha]_{Ia}/\alpha_I = -2{\cdot}62$. Inserting this value in the expression $\alpha_{II}/[\alpha]_{Ia} \times [\alpha]_{Ia}/\alpha_I \times \alpha_{III}/\alpha_{II}$ we derive from the value of α_{III}/α_I that the hydroperoxide is formed from the hydrogen phthalate with from +9·1 to +11·6% retention of configurational purity.

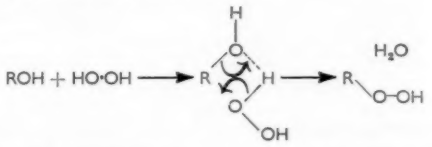
[5] Williams and Mosher, *J. Amer. Chem. Soc.*, 1954, **76**, 3495.
[6] Zeiss, *ibid.*, 1951, **73**, 2391.

Discussion

Any mechanism for the formation of 1-methyl-1-phenylpropyl hydroperoxide from the alcohol or from the hydrogen phthalate must be compatible with the observations that both reactions proceed by alkyl–oxygen fission, and that both give predominating retention of configuration.

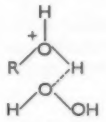
As there is no configuration-holding group in the 1-methyl-1-phenylpropyl structure, it would appear that both these reactions must proceed, at least in part, by an S_Ni mechanism.[7] This might reasonably be expected because the same structural factors in the reacting molecule appear to favour similarly the S_N1 and S_Ni mechanisms, and because the hydrogen peroxide molecule can form strong hydrogen bonds. Indeed we have postulated previously[3] a mechanism involving such hydrogen bond-assisted ionisation to account for the high reactivity of alcohols towards neutral hydrogen peroxide.

The alcohol would therefore appear to react by the mechanism shown in eqn. 1, in which the bond-breaking process is predominant.

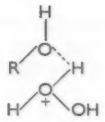


. . . . . (1)

Under acid conditions the reaction is accelerated with little change in the net stereochemical effect. The reacting species may now be represented by structures (IV) or (V), or by a hybrid of these two structures.

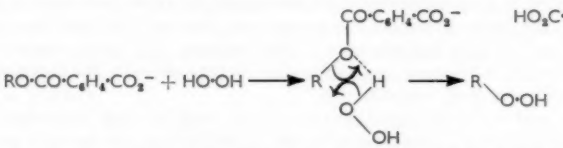


(IV)



(V)

There appears to be no clear precedent for a reaction of a carboxylic ester involving alkyl–oxygen fission by an S_Ni mechanism. The present example is illustrated in eqn. 2.



. . . . . (2)

In contrast, we found that 1 : 2 : 3 : 4-tetrahydro-1-naphthol and its hydrogen phthalate reacted with hydrogen peroxide with complete racemisation within the experimental error [8,*] and that 1-phenylethanol gave the hydroperoxide with predominating inversion of configuration (retention of configurational purity, −2·2 to −4·6%); its hydrogen phthalate did not react with hydrogen peroxide under our usual experimental conditions. We proposed an S_N1 mechanism for these reactions.

* Ikeda [9] has since resolved the hydroperoxide by asymmetric adsorption on (+)-quartz, and found that it had a specific rotatory power of at least $[\alpha]_D^{20}$ 20° (apparently in benzene). If we assume that the rotatory power does not differ greatly between a chloroform and a benzene solution, and that we could have measured a rotation of 0·02°, then the optical purity of the hydroperoxide from the alcohol and the hydrogen phthalate was not greater than 5% and 1·25% respectively. Our attempts to repeat Ikeda's resolution have as yet been unsuccessful.

[7] Cowdrey, Hughes, Ingold, Masterman, and Scott, *J.*, 1937, 1252; Dostrovsky, Hughes, and Ingold, *J.*, 1946, 173.
[8] Davies, Foster, and White, *J.*, 1953, 1541.
[9] Ikeda, *Bull. Liberal Arts Coll., Wakayama Univ.*, 1954, **4**, 27; *Chem. Abs.*, 1955, **49**, 9583.

Experimental

Unless otherwise stated, all values of α_D of liquids were recorded on the undiluted specimens in 1 dm. tubes at temperatures between 18° and 22°.

The usual explosion precautions were taken during the preparation of the hydroperoxides; no trouble in fact was encountered.

The resolution of the alcohol through its hydrogen phthalate has already been described.[2]

The Hydroperoxide from the Active Alcohol.—(i) *Acid conditions.* (+)-2-Phenylbutan-2-ol (2·79 g.), α_D +6·00°, was stirred for 6·5 hr. with 90% hydrogen peroxide (3 c.c.) containing sulphuric acid (1 drop). Water (6 c.c.) was then added, and the product extracted with pentane. The extract was washed with aqueous potassium carbonate and dried (Na_2SO_4). Distillation gave the (+)-hydroperoxide (1·9 g.), b. p. 53°/*ca.* 0·001 mm., n_D^{25} 1·5201, α_D^{20} +0·61°.

In a second experiment the (+)-alcohol (2·96 g.), α_D^{21} +6·24°, gave the (+)-hydroperoxide (1·5 g.), b. p. 75°/0·04 mm., n_D^{25} 1·5194, α_D^{20} +0·26°.

(ii) *Neutral conditions.* The alcohol (0·99 g.) α_D −11·62°, and 90% hydrogen peroxide (2 c.c.) were shaken at room temperature; iodimetric analysis showed the product to contain 30% of the hydroperoxide after 6 hr. and 46% after 18 hr. The alcohol–hydroperoxide mixture (0·642 g.) was added to acetic acid (5 c.c.) containing xanthhydrol (0·485 g.). 1-Methyl-1-phenylpropyl 9-xanthenyl peroxide (0·65 g.), m. p. and mixed m. p. 82°, α_D^{20} −1·07° (*l*, 2; *c*, 12·59 in chloroform), separated within 30 min.; a further small amount was recovered when the mother liquors were poured into water.

The Hydroperoxide from the Active Hydrogen Phthalate.—(−)-1-Methyl-1-phenylpropyl hydrogen phthalate (4·13 g.), $[\alpha]_D^{19\cdot5}$ −43° (*l*, 1; *c*, 15·1 in ethanol), in 90% hydrogen peroxide (10 c.c.) containing sodium hydrogen carbonate (2·1 g.) was kept at 0—10° for 18 hr. The combined products from two such reactions yielded the (+)-hydroperoxide (3·17 g.), b. p. 60—61°/*ca.* 0·001 mm., which after redistillation had b. p. 56°/*ca.* 0·001 mm., n_D^{25} 1·5198, α_{6563}^{18} +3·19°, α_D^{18} +4·05°, α_{5463}^{18} +4·83°. (Found: C, 72·9; H, 8·8. Calc. for $C_{16}H_{14}O_2$: C, 72·3; H, 8·4%).

The combined products from two similar preparations from the (−)-hydrogen phthalate (3·0 g.), α_D^{19} −15·0° (*l*, 1; *c*, 10·31 in ethanol) gave the (−)-hydroperoxide (1·66 g.), b. p. 64°/0·03 mm., n_D^{25} 1·5201, α_D^{19} +1·81°.

1-Methyl-1-phenylpropyl 9-Xanthenyl Peroxide.—The hydroperoxide (0·486 g.), α_D^{18} +4·05°, gave the crude peroxide which, after recrystallisation from aqueous ethanol, had (0·55 g.) m. p. 80—81°, $[\alpha]_D^{19}$ +3·40° (*l*, 1; *c*, 5·3 in chloroform).

Similarly a specimen of the hydroperoxide (0·4 g.), α_D^{19} +1·81°, gave the 9-xanthenyl derivative (0·59 g.; from ethanol), m. p. and mixed m. p. [with the (±)-compound] 82—82°, $[\alpha]_D^{19}$ +1·3° (*l*, 2; *c*, 5·8 in chloroform).

Reduction of the Hydroperoxide.—(i) *With sodium sulphite.* The hydroperoxide (1·60 g.), α_D^{19} +0·60°, was stirred with a solution of sodium sulphite heptahydrate (5·0 g.) in water (20 c.c.) at room temperature for 21 hr. A pentane extract gave the alcohol (1·15 g.), b. p. 75—80° (bath)/0·5 mm., n_D^{25} 1·5164, α_D^{18} +0·21° (Found: C, 80·0; H, 9·45. Calc. for $C_{16}H_{14}O$: C, 80·0; H, 9·4%).

(ii) *With zinc and acetic acid.* Zinc dust (2·0 g.) was added to a solution of the hydroperoxide (0·99 g.), α_D^{18} +4·05°, in acetic acid (5 c.c.). Water (1 c.c.) was then added dropwise with cooling. After 2 hr. the solution was diluted with water, neutralised with sodium hydrogen carbonate, and filtered from excess of zinc. An ethereal extract of the zinc and the filtrate gave the alcohol (0·70 g.), b. p. 75° (bath)/0·5 mm., n_D^{24} 1·5153, α_D^{18} +1·55°.

(iii) *With lithium aluminium hydride.* The hydroperoxide (0·65 g.), α_D^{18} +4·05°, was added dropwise to a stirred suspension of lithium aluminium hydride (0·17 g.) in ether (10 c.c.). The mixture was heated under reflux for 30 min., then treated with water and dilute sulphuric acid. The ethereal layer yielded the alcohol (0·35 g.), b. p. 80° (bath)/0·8 mm., $n_D^{24\cdot4}$ 1·5163, α_D^{19} +1·54°.

(iv) *With hydrogen and platinum.* Hydrogen was bubbled for 1·5 hr. through a solution of the hydroperoxide (0·96 g.), α_D^{18} +4·05°, in methanol (10 c.c.) containing reduced platinum oxide. The solution then gave a negative peroxide test; it was filtered and dried, yielding the alcohol (0·7 g.), b. p. 68°/0·4 mm., n_D^{25} 1·5162, α_D^{18} +1·55°.

The [^{18}O]*Alcohol and Its Hydrogen Phthalate.*—A solution of the alcohol (10 g.) in dioxan (70 c.c.), [^{18}O]water (0·87% enriched), and concentrated sulphuric acid (0·2 c.c.) was heated (steam bath) for 2 hr. Solid potassium carbonate was then added to neutralise the acid, and the bulk of the solvent removed by distillation. Pentane was added to the residue, the whole

shaken with solid potassium carbonate, and the small aqueous layer removed. The pentane solution was dried (K_2CO_3) and distilled giving a first fraction of the olefin (*ca.* 5 c.c.), followed by the alcohol (*ca.* 5 c.c.), b. p. 80° (bath)/0·4 mm. (Found: [^{18}O], 0·621% enriched). Its infrared spectrum was indistinguishable from that of the original alcohol.

A mixture of the [^{18}O]alcohol (3·07 g.), triethylamine (3·03 g.), and phthalic anhydride (3·03 g.) was stirred at 100° (bath) for 9·5 hr. By the usual method the hydrogen phthalate was isolated (2·50 g.), m. p. 110—112°. The isotopic constitution of the oxygen atom attached to the alkyl group was assumed to be the same as that in the alcohol.

The Hydroperoxide from the [^{18}O]*Alcohol.*—A mixture of the [^{18}O]alcohol (2 c.c.), 85% hydrogen peroxide (3 c.c.), and concentrated sulphuric acid (2 drops) was stirred at room temperature for 6·5 hr. The hydroperoxide was extracted into pentane in the usual way; the extract was stirred twice with 45% sodium hydroxide solution, and the sodium salt of the hydroperoxide was filtered off. The salt was washed thoroughly with pentane, then the hydroperoxide was regenerated from aqueous solution with carbon dioxide. The hydroperoxide was extracted into pentane and the solvent removed. The hydroperoxide smelled of phenol; a fraction (0·49 g.) was therefore treated with xanthhydrol (0·585 g.) giving 1-methyl-1-phenylpropyl 9-xanthenyl peroxide, m. p. and mixed m. p. 83·5—84° (0·42 g.), which was isotopically normal.

The Hydroperoxide from the Hydrogen Phthalate of the [^{18}O]*Alcohol.*—The powdered [^{18}O]ester (2·50 g.) was added to a solution of sodium hydrogen carbonate (1·75 g.) in 85% hydrogen peroxide (10 c.c.) at 0°. The oil which separated was collected in pentane in the usual way, and the solvent removed at 50°/0·04 mm., giving the hydroperoxide which was isotopically normal.

I am indebted to Professor E. D. Hughes, F.R.S., Sir Christopher Ingold, F.R.S., and Dr. J. Kenyon, F.R.S., for their interest and encouragement, to Dr. Kenyon and Dr. L. W. F. Salamé for the generous gift of the optically active compounds and to Dr. C. A. Bunton and Professor D. R. Llewellyn for carrying out the isotopic measurements.

William Ramsay and Ralph Forster Laboratories,
University College, Gower Street, London, W.C.1. [*Received, February 28th,* 1958.]

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701. *The Crystal Structure of Dichlorobisthioureazinc.*

By N. R. Kunchur and Mary R. Truter.

An *X*-ray crystal structure analysis of dichlorobisthioureazinc, $[(NH_2)_2CS]_2ZnCl_2$, has shown that the complex is molecular, each zinc atom being tetrahedrally co-ordinated to two chlorine and two sulphur atoms. Three-dimensional refinement, with allowance for anisotropic thermal motion, gave the bond lengths Zn–Cl = 2·32 ± 0·01 Å, Zn–S = 2·35 ± 0·01 Å, S–C = 1·78 ± 0·02 Å, C–N = 1·28 ± 0·03 Å. The thiourea group is planar with angles S–C–N 121·2° ± 1·6° and 116·1° ± 1·6° and N–C–N 122·6° ± 2·0°. The bond angle Zn–S–C is 108·6° ± 0·7°. The zinc valency angles deviate slightly but significantly from the tetrahedral, the angles being Cl–Zn–Cl 107·3°, S–Zn–S 111·5°, S–Zn–Cl 109·0° and 110·6°, all ±0·2°.

Most of the known complexes of zinc are tetrahedral, but there are exceptions, *e.g.*, five-covalent dichloroterpyridylzinc.[1] Dichlorobisthioureazinc, $[(NH_2)_2CS]_2ZnCl_2$, could be either a molecular compound or a salt, or, since the thiourea ligands might be linked through either the sulphur or the nitrogen atoms, it could be polynuclear. It is sparingly soluble in hot water and its aqueous solution does not give a precipitate with silver nitrate, so it is likely that the chlorine is covalently linked. Although both sulphur and nitrogen atoms form co-ordinate links with zinc, the majority of ligands containing both atoms are linked through the sulphur; hence the molecule is probably neutral with the zinc tetrahedrally bound to two chlorine and two sulphur atoms. This arrangement has, in fact, been proved by the structure analysis described below.

[1] Corbridge and Cox, *J.*, 1956, 594.

As the crystal structure of thiourea has recently been accurately re-determined [2] the analysis of the structure of the zinc complex has been carried as far as possible to see if any conclusions could be drawn from changes in the molecular dimensions of thiourea on co-ordination.

Experimental

Crystals of dichlorobisthioureazinc were obtained by Maly's method: [3] hot saturated aqueous solutions of zinc chloride and thiourea were mixed, and cooled to give acicular crystals of the complex (Found: Zn, 22·9; Cl, 24·0; N, 20·4. Calc. for $ZnS_2Cl_2C_2H_8N_4$: Zn, 22·6; Cl, 24·8; N, 19·5%).

Accurate determination of the dimensions of the orthorhombic unit cell by Straumanis's method, Cu-K radiation being used, gave $a = 13{\cdot}065$, $b = 12{\cdot}722$, $c = 5{\cdot}890$ Å, all $\pm 0{\cdot}005$ Å ($v = 978{\cdot}92$ Å^3). The density calculated for 4 molecules (M, 288·6) per unit cell is 1·960 g./c.c., in satisfactory agreement with the value 1·965 g./c.c. obtained by flotation.

Reflections from the classes of planes $(0kl)$ with $k + l = 2n + 1$ and $(hk0)$ with $h = 2n + 1$ were absent systematically. This is consistent with the space groups $Pnma$—D_{2h}^{16} and $Pn2_1a$—C_{2v}^{9}. A piezoelectric test gave a negative result, and a centric distribution [4] was found for the intensities of the $(hk0)$ planes, so that the space group was taken to be the centrosymmetrical $Pnma$.

For intensity measurements very small crystals (0·03 mm. in diameter) were photographed with Cu-K radiation, and no absorption correction was made (linear absorption coefficient, 127 cm.$^{-1}$). Equi-inclination Weissenberg photographs were taken about the principal axes for as many layers as possible, *viz.* up to $(hk3)$, $(7kl)$, and $(h7l)$. Of the possible 739 reflections, 567 were observed. Intensities were estimated visually by comparison with a calibration slip, corrected for Lorentz and polarisation factors with the aid of a Cochran chart, and were correlated, and the resulting F^2 scaled by comparison with the absolute values of F^2 $(hk0)$ determined by Wilson's method.[5] The square roots were extracted to give $|F_{obs}|$ and during the isotropic refinement a more accurate scale factor was obtained by making $\sum|F_{obs}| = \sum|F_{calc}|$, allowing for multiplicity, and during anisotropic refinement the scale factor was one of the parameters.

[Nardelli, Cavalca, and Braibanti [6] determined the unit-cell dimensions and space group, obtaining unit-cell dimensions not significantly different from ours, but a different space group because on their photographs there is a very weak reflection corresponding to (0,11,0) which violates the absences required for the n-glide but probably actually arises from double reflection by the pairs of planes $(\bar{2}40)$, (270) and (240), $(\bar{2}70)$.]

Three-dimensional Structure Analysis.—An approximate structure was obtained by two-dimensional methods, the projections along [001] and [010] being solved by Patterson and Fourier syntheses and refined until R was less than 0·22, where $R = \sum|(|F_{obs}| - |F_{calc}|)|/\sum|F_{obs}|$. The zinc and chlorine atoms lie in mirror planes at $y = 1/4$ and $3/4$; the thiourea molecules are in general positions, related in pairs by the mirror planes. The structure is shown in the Figure; each zinc atom is surrounded approximately tetrahedrally by two chlorine and two sulphur atoms.

Three-dimensional refinement of co-ordinates was by differential syntheses with a back-shift correction for finite series errors. Temperature factors were refined by changing the value of B in the exponential $-(B \sin^2\theta/\lambda^2)$ for each atom to make equal the curvatures of the electron-density distributions, $\partial^2\rho/\partial x_i^2$, derived from the observed and calculated structure factors.

The first set of three-dimensional structure factors was calculated from the co-ordinates given by the two-dimensional analysis with scattering factors for carbon and nitrogen (McWeeny [8]), chlorine and zinc (Berghuis *et al.*[9]) and sulphur (International Tables [10]) all

[2] Kunchur and Truter, *J.*, 1958, 2551.
[3] Maly, *Ber.*, 1876, **9**, 172.
[4] Howells, Phillips, and Rogers, *Research*, 1949, **2**, 338.
[5] Wilson, *Acta Cryst.*, 1949, **2**, 318.
[6] Nardelli, Cavalca, and Braibanti, *Gazzetta*, 1956, **86**, 1037.
[7] Nardelli and Cavalca, personal communication.
[8] McWeeny, *Acta Cryst.*, 1951, **4**, 513.
[9] Berghuis, Ijbertha, Haanappel, Potters, Loopstra, MacGillavry, and Veenendaal, *ibid.*, 1955, **8**, 478.
[10] "International Tables for the Determination of Crystal Structures," Borntraeger, Berlin, 1935.

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with $B = 1{\cdot}95$ Å^2; these gave $R = 0{\cdot}30$. It was found that the temperature factor was correct for zinc but low for all the other atoms. Five cycles of refinement were required to reduce R to 0·182 and the last differential synthesis gave no shifts as large as the standard deviations so that isotropic refinement was complete. However, examination of the ratios between the observed curvatures and those calculated on the assumption of isotropic thermal motion shows that even for the heavy atoms the motions are markedly anisotropic. In Table 1 are shown the values of B used for the last isotropic calculation of structure factors, the observed peak electron density, ρ, the ratio between this and the calculated value, and $r(x_i) = (\partial^2\rho_o/\partial x_i^2)/(\partial^2\rho_c/\partial x_i^2)$.

TABLE 1.

	B, Å^2	ρ, e/Å^3	ρ_o/ρ_c	$r(x)$	$r(y)$	$r(z)$
Zn	2·10	64·1	0·95	0·90	1·00	0·95
S	2·60	29·6	0·96	0·87	1·03	0·99
Cl^1	2·50	31·1	0·96	0·94	0·90	0·98
Cl^2	2·50	28·8	0·91	0·75	1·02	0·93
C	2·50	8·0	1·00	0·96	0·99	1·02
N^1	3·20	8·2	0·89	0·78	0·91	0·90
N^2	3·20	7·6	0·90	0·75	1·03	0·87
	Weighted mean		0·95	0·86	0·99	0·96
					0·94	

The ratios correspond to values of $|F_{obs}|$ scaled to make $\sum|F_{obs}| = \sum|F_{calc}|$.

An interesting feature is the effect of anomalous dispersion on the temperature factor for zinc. From the atomic masses the ratio $B_{Zn} : B_{Cl}$ should be about 0·49 : 1·0 while that found is 0·84 : 1·0. Structure factors for the axial reflections were calculated with the correction for anomalous dispersion given by Dauben and Templeton [11]; a plot of log $([F_{corr}]/[F_{uncorr}])$ against $\sin^2\theta$ was linear and from the slope the value of the artificial temperature factor which allowed for anomalous dispersion was found to be $B = 0{\cdot}65$ Å^2. The value $B = 2{\cdot}10$ Å^2 empirically determined for zinc already includes this correction, $B = 0{\cdot}65$ Å^2, so that the contribution due to the thermal vibration of zinc is $B' = 1{\cdot}45$ Å^2. The $B'_{Zn} : B_{Cl}$ ratio is 0·58 : 1·0, in better agreement with expectation.

Anisotropic Refinement.—Cruickshank's method [12] for the successive refinement of anisotropic thermal parameters was used. The equations, which he gives, lead to the correct coefficients b_{ij} for each atom in the expression for the temperature factor exp $-(b_{11}h^2 + b_{12}hk + b_{13}hl + b_{22}k^2 + b_{23}kl + b_{33}l^2)$. Co-ordinates were refined by differential synthesis as before. The scale factor was refined to make the peak electron densities derived from the observed and calculated structure factors equal; this at first was different from the factor required to make $\sum|F_{obs}| = \sum|F_{calc}|$ allowing for multiplicity, but when refinement was complete the two factors were the same. The first set of structure factors calculated with allowance for anisotropy gave $R = 0{\cdot}153$; co-ordinate, and temperature factor shifts were applied to give new parameters (all $\times 10^5$), shown below, for which $R = 0{\cdot}148$.

	x/a	y/b	z/c	b_{11}	b_{12}	b_{13}	b_{22}	b_{23}	b_{33}
Zn	0·16666	0·25000	0·31558	390	0	94	242	0	1598
S	0·09567	0·09791	0·15584	555	$\bar{2}6\bar{2}$	$\bar{5}8\bar{7}$	269	134	1619
Cl^1	0·34102	0·25000	0·25161	322	0	17	515	0	1588
Cl^2	0·14580	0·25000	$\bar{0}{\cdot}\bar{2}\bar{5}4\bar{2}8$	776	0	812	245	0	1875
C	0·11794	$\bar{0}{\cdot}\bar{0}0\bar{8}1\bar{1}$	0·34335	365	67	$\bar{3}\bar{2}0$	390	$\bar{3}\bar{3}3$	1210
N^1	0·14287	0·00597	$\bar{0}{\cdot}\bar{4}\bar{4}5\bar{7}1$	757	$\bar{3}\bar{4}0$	$\bar{2}\bar{7}5$	555	$\bar{9}\bar{4}2$	2612
N^2	0·10494	$\bar{0}{\cdot}\bar{0}9\bar{8}7\bar{1}$	0·26297	769	$\bar{1}0\bar{5}$	$\bar{1}0\bar{4}\bar{6}$	324	573	3313

(This table gives the parameters actually used although not all the figures are significant.) A list of structure factors calculated from these parameters is given in Table 2 together with the observed structure factors.

Differential syntheses based on the structure factors in Table 2 indicated a maximum shift of 0·017 Å in y_O and a corresponding standard deviation of 0·023 Å so that anisotropic refinement of co-ordinates was complete. The mean electron density ratio was 1·005, the mean curvature ratio 0·995, and the average deviation of the ratios from unity 1%; comparison with the values

[11] Dauben and Templeton, *Acta Cryst.*, 1955, **8**, 841.
[12] Cruickshank, *ibid.*, 1956, **9**, 747.

in Table 1 shows the improvement effected by anisotropic refinement. From the small differences between the observed and calculated curvatures the final changes in the thermal parameters were calculated, the largest (in b_{13} for Cl[2]) being 1·2 times the corresponding standard deviation calculated from Cruickshank's formula.[12] Application of the shifts to the co-ordinates and temperature factors gave the final parameters which are shown in Table 3; the thermal parameters are quoted as the mean square amplitudes of vibration, U, where $U_{ii} = a_i^2 b_{ii}/2\pi^2$ and $U_{ij} = a_i a_j b_{ij}/4\pi^2$ $(i \neq j)$, the a's being unit-cell dimensions. Table 3 also shows the peak electron densities for the atoms; the standard deviation, σ (ρ), was 0·5 e/Å^3. In Table 3 the estimated standard deviations [13] in the co-ordinates, σ (x_i), are given; for the thermal parameters, the values of $\sigma(U_{ij})$ derived from $\sigma(b_{ij})$ were found to be approximately the same for all i and j for each atom so that only a mean $\sigma(U)$ is quoted.

Correction for Rotational Oscillation.—It has been shown [14] that rotational oscillations can cause appreciable errors in apparent atomic positions, and for some molecules which can be assumed to be rigid the thermal motions can be analysed [15] to give the translational and

TABLE 2. *Observed and calculated structure factors.*

Reflections which are too weak to be observed have been omitted.

hkl	F (calc.)	F (obs.)	hkl	F (calc.)	F (obs.)	hkl	F (calc.)	F (obs.)	hkl	F (calc.)	F (obs.)	hkl	F (calc.)	F (obs.)	hkl	F (calc.)	F (obs.)
000	(576)	—	10,0,0	−18	21	571	29	31	292	24	24	103	9	12	13,2,3	−19	17
020	−92	76	10,1,0	32	29	591	−24	31	2,10,2	−39	44	113	−58	53	13,3,3	31	28
040	168	138	10,2,0	69	61	5,11,1	13	19	2,11,2	−31	27	123	−57	47			
060	−198	169	10,4,0	−87	63	5,12,1	−11	17	2,12,2	18	16	133	116	79	024	−49	52
080	173	154	10,7,0	−30	23	5,13,1	−17	23	2,13,2	23	24	143	86	65	044	42	36
0,12,0	114	99	10,8,0	−37	32				2,14,2	−13	9	153	−60	38			
0,14,0	−77	64	10,10,0	59	42	701	−54	46	2,15,2	−21	13	173	39	35	204	−24	19
0,16,0	24	21	10,12,0	−17	10	711	40	47				183	29	28	214	43	56
						741	−26	31	402	110	91	193	−61	64	234	22	23
200	−53	51	12,0,0	57	54	751	23	31	412	−28	26	1,10,3	−53	60	254	12	17
210	−129	108	12,1,0	−7	16	761	10	10	422	−73	71	1,11,3	53	60	274	−48	42
220	101	94	12,2,0	−54	41	771	−36	38	432	40	49						
230	46	34	12,3,0	−12	16	781	−28	34	442	36	35	303	−75	71	424	35	41
240	−116	125	12,4,0	26	27	7,12,1	−15	7	452	−30	31	313	27	28	434	37	31
250	−82	94	12,6,0	−57	48	7,13,1	23	26	462	−87	89	323	87	72	444	−26	29
260	34	33	12,7,0	12	14				472	20	16	333	70	76	454	−12	12
270	102	87	12,8,0	36	39	901	33	36	482	51	63	343	−87	88			
280	−46	49	12,10,0	−23	26	911	16	24	492	−26	27	363	57	38	604	49	40
290	−32	27				921	−19	22	4,10,2	−22	27	373	−31	21	614	−14	21
2,10,0	59	54	14,0,0	−17	23	931	13	18	4,11,2	24	27	383	−59	62	634	−17	23
2,11,0	36	27	14,8,0	−2	5	961	−32	37	4,12,2	37	41	393	−29	36			
2,12,0	−27	23				971	−16	13	4,13,2	−12	31	3,10,3	53	56	804	−6	16
2,13,0	−60	50	16,0,0	−30	17	981	14	13	4,14,2	−32	28	3,11,3	25	23	834	−39	29
2,16,0	−27	19	16,2,0	20	16	9,12,1	15	19				3,12,3	−36	38	854	10	12
						9,13,1	12	10	602	−52	42	3,13,3	25	26			
400	−288	223	101	−32	36				622	112	104	3,14,3	28	26	10,04	−37	30
410	45	38	111	31	35	11,0,1	17	14	642	−98	97						
420	25	24	131	−74	83	11,1,1	−18	17	662	59	67	503	60	60	105	−27	21
430	−97	86	141	−86	91	11,2,1	16	14	682	−50	64	513	74	73	115	46	51
440	−88	79	151	38	47	11,3,1	7	7	6,10,2	71	73	523	−20	26	125	30	37
450	61	59	161	−25	28	11,4,1	−7	10	6,12,2	−32	36	533	−60	65	135	−50	48
460	106	91	181	−26	28	11,5,1	−16	14	6,14,2	24	22	543	−22	26	145	−32	29
470	−21	23	191	40	34	11,6,1	−1	1				553	53	47	155	44	33
480	−100	100	1,10,1	26	20	11,7,1	15	15	802	11	8	563	−60	47	175	−33	25
490	59	59	1,11,1	−25	21	11,10,1	15	21	812	17	13	573	−64	65	195	37	36
4,11,0	−45	45	1,12,1	−11	13	11,11,1	8	7	822	−15	23	583	17	16			
4,12,0	−71	39	1,13,1	6	8				832	−28	31	593	38	18	305	54	49
4,14,0	43	42	1,15,1	−15	15	13,2,1	7	10	842	15	18				325	−49	51
			1,16,1	−18	17	13,3,1	−20	21	852	18	19	703	57	54	335	−17	26
600	73	69				13,4,1	−5	7	862	−8	9	713	−64	63	345	47	46
610	18	22	301	85	89	13,9,1	10	13	8,13,2	8	16	723	−32	38	365	−44	40
620	−150	128	311	−23	32							743	20	23			
640	181	171	321	−12	15	002	−205	179	10,0,2	20	21	753	−43	42	505	−15	23
650	16	17	331	−50	60	022	140	124	10,1,2	−16	21	763	−43	46	515	−49	52
660	−51	52	341	84	107	042	−72	64	10,2,2	−56	50	773	55	46	535	35	35
670	−18	21	371	27	24	062	150	124	10,4,2	47	46	783	35	26	555	−40	33
680	78	68	381	47	42	082	−90	85	10,6,2	−28	35				575	39	33
6,10,0	−106	85	391	22	21	0,10,2	44	53	10,7,2	14	8	903	−49	49	595	−30	28
6,12,0	45	43	3,10,1	−20	21	0,12,2	−61	50	10,8,2	25	29	913	−27	29	705	−33	28
6,14,0	−23	16	3,11,1	−12	10	0,14,2	55	46	10,10,2	−40	44	923	41	45	715	27	26
			3,12,1	23	25							933	−14	16	725	23	19
810	−23	17	3,13,1	−16	23	202	33	29	12,0,2	−41	40	963	56	51	735	−21	17
820	52	47				212	43	45	12,2,2	36	29						
830	74	63	501	−34	36	222	−69	62	12,4,2	−25	25	11,1,3	32	32	905	22	22
850	−39	30	511	−43	54	232	−51	51	12,6,2	37	39	11,2,3	−15	25	925	−26	26
860	23	30	521	18	17	242	59	58	12,8,2	−26	30	11,3,3	−19	23			
890	−49	39	531	31	36	252	36	38	12,10,2	18	16	11,4,3	23	25	11,3,5	23	17
8,10,0	27	22	541	26	27	262	−35	43				11,5,3	30	26			
8,11,0	34	22	551	−32	34	272	−45	45				11,7,3	−25	31	006	39	45
8,13,0	−6	12	561	45	34	282	29	27	16,0,2	20	16						

[12] Cruickshank and Robertson, *Acta Cryst.*, 1953, **6**, 698.
[14] Cox, Cruickshank, and Smith, *Nature*, 1955, **175**, 766.
[15] Cruickshank, *Acta Cryst.*, 1956, **9**, 754.

TABLE 3. (*Continued.*)

hkl	F (calc.)	F (obs.)	hkl	F (calc.)	F (obs.)	hkl	F (calc.)	F (obs.)	hkl	F (calc.)	F (obs.)	hkl	F (calc.)	F (obs.)	hkl	F (calc.)	F (obs.)
216	−53	63	401	−57	59	10,6,1	−30	24	392	−31	37	033	−63	48	344	−25	24
256	−33	38	411	45	54	10,8,1	21	20	3,10,2	−26	34	053	30	17	354	27	22
276	51	41	421	−42	48	10,9,1	27	34	3,11,2	23	28				364	−37	38
			431	−18	19	10,10,1	−16	20	3,12,2	−14	16	213	−23	19			
406	−22	26	441	52	54				3,14,2	21	24	223	46	43	504	46	43
416	18	17	451	28	34	12,0,1	−48	40	3,15,2	17	13	233	11	14	514	−46	48
436	−45	41	461	13	21	12,1,1	−54	41				243	−20	24	544	30	29
456	26	30	471	−43	41	12,3,1	30	32	502	−32	25	253	−15	21	554	−26	12
			4,10,1	−44	31	12,5,1	−40	36	512	68	68	263	31	27	574	45	39
626	−13	14	4,11,1	−14	17	12,6,1	29	27	522	34	45						
			4,13,1	18	20	12,7,1	45	34	532	29	36	403	12	14	704	−47	45
836	42	28				12,8,1	−18	17	542	−20	29	423	−23	28	714	−15	21
			601	18	22	12,9,1	−28	28	552	36	40	433	36	38	724	34	32
10,0,6	17	16	611	−64	63	12,10,1	−5	7	562	29	31	453	−14	19	734	−12	11
			621	54	57	12,11,1	15	14	572	−59	59	463	−18	19	764	47	41
107	22	18	631	105	110				582	−23	33						
117	−19	19	641	−44	36	14,0,1	−12	10				613	40	42	904	−14	16
			651	−69	56	14,1,1	16	10	702	67	51	623	−22	27	914	35	37
307	−18	16	671	30	28	14,3,1	−10	10	712	22	22	633	−17	26	924	−23	29
			691	−60	34	14,4,1	11	7	722	−37	43	653	26	31			
527	−4	12	6,10,1	40	24	14,5,1	15	7	762	−68	69	663	−19	24	11,0,4	17	16
			6,11,1	45	34	14,6,1	16	7	772	−26	29	673	−32	31	11,2,4	−20	29
011	−125	106	6,13,1	−13	16	14,7,1	−15	7	782	24	32				11,3,4	35	32
031	62	69	6,15,1	19	17				7,12,2	25	23	813	−19	22			
051	−75	76				16,0,1	19	10	7,14,2	−27	21	823	28	32	035	40	40
071	96	89	801	60	64	16.1.1	22	21				843	−12	17			
091	−25	30	811	46	51				902	13	17	863	24	20	205	87	77
0,11,1	30	24	821	46	33	102	0	13	912	−47	38	873	20	17	235	17	18
0,13,1	−42	36	831	−34	34	112	−23	28	922	14	9				245	36	29
0,15,1	19	19	841	−31	34	122	−51	48	942	−29	38	10,1,3	−22	24	265	−39	28
			851	34	36	132	−80	70	952	−36	36	10,7,3	19	20			
201	−115	96	861	−29	38	142	64	64	962	−10	9				405	−17	18
211	46	48	871	−32	38	172	24	29	972	38	46	12,1,3	20	25	415	−16	17
221	−72	96	881	11	13	182	21	34	9,10,2	21	24	12,2,3	−18	17	425	37	37
231	−67	89	891	31	40	192	33	38				12,3,3	−18	24	435	−34	31
241	72	96	8,10,1	34	39	1,10,2	−42	44	11,0,2	−21	29				445	−49	45
251	45	48	8,11,1	−13	10	1,11,2	−26	28	11,2,2	25	22	104	−33	30			
261	54	49	8,12,1	11	13	1,13,2	−22	26	11,3,2	−42	38	114	6	10	605	−27	26
271	−22	22	8,13,1	20	21	1,15,2	−12	10	11,5,2	17	21	124	20	21	625	−14	10
281	−18	19	8,14,1	−10	10				11,6,2	33	38	134	44	50	635	−30	25
291	35	31				302	−62	64	11,9,2	26	28	144	−58	58			
2,10,1	−51	40	10,0,1	27	21	312	−32	24	11,11,2	−19	16	154	−10	17	825	−36	29
2,11,1	−27	24	10,1,1	16	14	332	58	52							835	13	17
2,12,1	−20	23	10,2,1	−32	36	342	43	55	13,2,2	−25	24	304	26	32	845	44	42
2,13,1	9	13	10,3,1	−43	34	352	−30	31	13,4,2	32	34	314	31	27			
2,14,1	18	19	10,4,1	13	14	362	53	60				324	−12	16	10,2,5	25	25
2,15,1	−11	15	10,5,1	21	24	372	24	28	013	18	19	334	−56	31			
2,16,1	18	17															

TABLE 3. *Final parameters and estimated standard deviations.*

	x/z	*y/b*	*z/c*	*X* (Å)	*Y* (Å)	*Z* (Å)	$\sigma(x)$ (10^3 Å)	$\sigma(y)$ (10^3 Å)	$\sigma(z)$ (10^3 Å)
Zn	0·1668	0·2500	0·3154	2·179	3·181	1·858	2	—	2
S	0·0959	0·0978	0·1560	1·253	1·244	0·919	5	5	5
Cl^1	0·3409	0·2500	0·2519	4·454	3·181	1·484	4	—	4
Cl_2	0·1458	0·2500	−0·2946	1·905	3·181	4·155	6	—	4
C	0·1177	−0·0095	0·3447	1·537	−0·120	2·030	15	23	19
N^1	0·1431	0·0062	0·5551	1·870	0·079	3·269	20	18	17
N^2	0·1043	−0·0995	0·2638	1·363	−1·265	1·554	20	15	22

	U_{11} (10^3 Å^2)	U_{13} (10^3 Å^2)	U_{13} (10^3 Å^2)	U_{23} (10^3 Å^2)	U_{23} (10^3 Å^2)	U_{23} (10^3 Å^2)	$\sigma(U)$ (10^3 Å^2)	ρ (e/Å^3)
Zn	34	0	3	20	0	28	2	65·6
S	49	−26	−26	21	5	28	4	30·6
Cl^1	27	0	0	43	0	28	4	32·2
Cl^2	73	0	26	17	0	33	4	30·0
C	33	3	−11	31	−7	22	17	8·9
N^1	66	−33	−23	43	−36	47	19	8·9
N^2	67	−15	−40	24	23	63	19	8·3

rotational vibrations. A rigorous analysis for this complex is not possible because it is unlikely to be rigid and the standard deviations in the mean square amplitudes of oscillation are very large for the light atoms; it is, however, of interest to find an approximate value for the *maximum* correction for rotational oscillation. The procedure used was the same as that described for the ethyl sulphate anion [16] so that only the outline is given here. Cruickshank [17]

[16] Truter, *Acta Cryst.*, 1958, in the press.
[17] Cruickshank, *ibid.*, 1956, **9**, 757.

has shown that the approximate correction, M, to the length OP from the mass centre O to an atom P is $M = (U_a + U_b)/2OP$ where U_a and U_b are the mean square amplitudes of oscillation about two axes through O orthogonal to OP. The zinc atom is only 0·2 Å from the mass centre of the molecule so that the motion of this atom may be taken as approximately the translational motion of the molecule as a whole. Subtraction of the thermal parameters for zinc (allowing for an apparent mean square amplitude of 8×10^{-3} Å^2 due to anomalous dispersion) gave mean square amplitudes, $U-U_{Zn}$, for the other atoms, which for the purpose of finding the maximum correction were taken as entirely due to rotational oscillation. The maximum, minimum, and intermediate values of the " oscillation " mean square amplitudes and their directions were calculated for each atom; the magnitudes are:

	S	Cl^1	Cl^2	C	N^1	N^2
$U_{max.}$ (10^3 Å^2)	37	32	65	20	53	67
$U_{min.}$ (10^3 Å^2)	0	1	5	5	0	8
$U_{inter.}$ (10^3 Å^2)	4	8	9	11	45	21

U_a was taken to be $U_{max.}$. For those atoms, Cl and S, for which $U_{max.}$ was approximately perpendicular to OP, U_b was taken to be the value of U in the third orthogonal direction, and a reliable correction was obtained. For the light atoms U_b was taken to be $U_{inter.}$; this procedure may overestimate M and probably underestimates the correction to the C–N bond length because it is likely that the nitrogen atoms rotate about the C–S bond axis, as in thiourea itself, as well as about the mass centre of the molecule. Corrected co-ordinates were obtained by increasing the distance of each atom from the mass centre by M along OP.

Interatomic Distances and Angles.—The bond lengths, with and without corrections for rotational oscillation, and their estimated standard deviations (e.s.d.) are shown in Table 4; as can be seen from the values of $\sigma(U)$ in Table 3, even if the procedure were rigorous some uncertainty in the corrections would be introduced by the inaccuracies in the thermal parameters so that for the final values the limits of error have been increased to allow for these deficiencies. Only one set of bond angles is given because they were not altered by the corrections. Some of the intramolecular non-bonded distances are also given in Table 4. In the Figure the intramolecular separations between nearest neighbours are shown. The thiourea group is planar to within ±0·01 Å as in thiourea.[2]

TABLE 4. *Interatomic distances and angles.*

Bond lengths	uncorr. Å	corr. Å	e.s.d. Å	final Å	Bond angles		e.s.d.	Distance	Å
Zn–S	2·343	2·352	0·005	2·35 ± 0·01	S–Zn–S′	111·5°	0·2	S...N^1	2·69
Zn–Cl^1	2·305	2·314	0·005	2·31 } 2·32 ± 0·01	S–Zn–Cl^1	109·0	0·2	S...N^2	2·59
Zn–Cl^2	2·313	2·328	0·005	2·32 }	S–Zn–Cl^2	110·6	0·2	N^1..N^2	2·24
S–C	1·78	1·78	0·022	1·78 ± 0·02	Cl^1–Zn–Cl^2	107·3	0·2	S...S′	3·87
C–N^1	1·30	1·30	0·027	1·30 } 1·28 ± 0·03	Zn–S–C	108·6	0·7	Cl^1.Cl^2	3·69
C–N^2	1·25	1·26	0·028	1·26 }	S–C–N^1	121·2	1·5	Zn..C	3·36
					S–C–N^2	116·1	1·5	N^1.Cl^2	3·23
					N^1–C–N^2	122·6	1·9		

It is noteworthy that even for bonds between heavy atoms the systematic error due to rotational oscillations may be twice the estimated standard deviation calculated to allow for random errors.

DISCUSSION

The structure as a whole is shown in the Figure. The packing is very efficient and there are many separations of about 3·5—4·0 Å but no unreasonably short ones and none that can be attributed to hydrogen bonding.

The significant departure of the bond angles around the zinc atom from those of a regular tetrahedron may indicate that the bonds are not formed from simple sp^3 hybrid orbitals but include some contribution from the d orbitals, or it may give rise to more efficient packing of the molecules in the solid. The Zn–S bond is not significantly longer than that in zinc blende but the Zn–Cl bond, which is the same as that (2·29 ± 0·02 Å) found in dichloroterpyridylzinc,[1] is significantly shorter than the sum of the ionic radii

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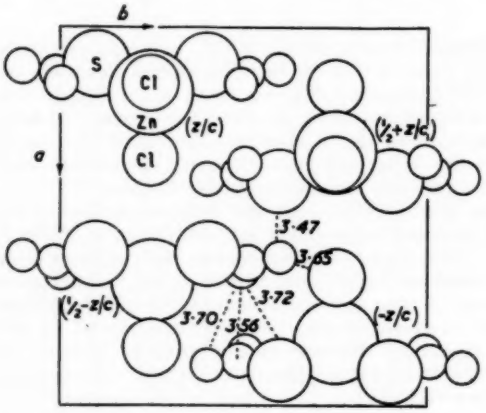
(2·66 Å) as given by the separation in zinc chloride. Probably all the bonds to the zinc atom are partly ionic and partly covalent.

The S–C bond does not differ significantly from the value generally accepted for a single bond, 1·82 Å. A large variation in the bond angles for sulphur bonded to two other atoms has been observed [18] ranging from 65·8° to 119·0°; the angle found in the complex, 108·6° is approximately tetrahedral.

Comparison with unco-ordinated thiourea [2] shows that the molecule has retained its planarity, *i.e.*, that the carbon atom is in a state of sp^2 hybridisation. The C–S bond is lengthened and the C–N bonds are shortened. The change in the C–S bond is just significant; the bond in thiourea is 1·71 ± 0·01 Å, so that the probability that the increase of 0·07 Å has occurred as a result of random errors of observation is 1 in 100. The very large standard deviations in the C–N bond lengths mean that the difference between



Projection along [001]. *The heights of the molecules along the* c *axis are shown as fractional co-ordinates in parentheses. The numbers are distances in* Å *between nitrogen atoms and their nearest neighbours as indicated by the dotted lines.*

1·28 ± 0·03 Å in the complex and 1·33 ± 0·01 Å in the molecule is not statistically significant. Qualitatively the changes appear reasonable; in thiourea three forms, two zwitterionic [$NH_2 \cdot NH_2^+ \cdot C \cdot S^-$] and one uncharged [$(NH_2)_2C{:}S$], contribute to the bonding; a longer carbon-sulphur bond in the complex implies a greater contribution from the zwitterionic forms with more double-bond character for the carbon–nitrogen bonds. A very simple postulate is that the sulphur hybridisation is sp^2 in thiourea with an electron in a p_z orbital delocalised to participate in the π-bonding system of the molecule whereas in the complex, as in zinc blende, the sulphur atom is in sp^3 hybridisation. In the complex the angles round the carbon atom do not differ significantly from 120°, but they do differ significantly from those in thiourea for which S–C–N = 122·2° ± 0·6° and N–C–N = 115·6° ± 1·1°. The significance of these changes will be discussed later in connection with work now in progress [19] on thioacetamide and some of its co-ordination compounds.

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Department of Inorganic and Structural Chemistry,
The University of Leeds. [*Received, March* 21*st*, 1958.]

[18] Abrahams, *Quart. Reviews*, 1956, **10**, 407.
[19] Truter, *Acta Cryst.*, 1957, **10**, 785.

702. *The Reaction of Tetramethyl-lead and Trimethyl-lead Chloride with Alkali Metals in Liquid Ammonia.*

By A. K. Holliday and G. Pass.

Alkali metals in liquid ammonia produce fission of one Pb–C bond in $PbMe_4$, giving $PbMe_3^-$ ions and methyl radicals; the latter yield methane and ethane. The $PbMe_3^-$ ions are then solvolysed; in presence of potassium all the methyl groups are removed to give lead imide, while with sodium or lithium only one is removed, giving dimethyl-lead. With trimethyl-lead chloride, $PbMe_3^-$ is first formed; some of this suffers fission of all Pb–C bonds, some forms the ion $PbMe_2^-$ (which is then solvolysed), and some undergoes disproportionation.

In a previous paper [1] it was shown that potassium and a tetra-alkylammonium ion in liquid ammonia give a tertiary amine and a hydrocarbon; the mechanism suggested was:

$$NR_4^+ + e^- \longrightarrow NR_3 + R$$
$$R + e^- \longrightarrow R^-$$
$$R^- + NH_3 \longrightarrow RH + NH_2^-$$

When R = Me, a small amount of ethane was also formed, by combination of two methyl radicals or by a reaction $NMe_4^+ + Me^- \longrightarrow NMe_3 + C_2H_6$. It seemed that, if reaction of a metal–ammonia solution with a neutral molecule of type MMe_4 could yield ethane, then radical combination must be operative; hence a study of the reaction of tetramethyl-lead has been undertaken.

Reductions of lead tetra-alkyls in liquid ammonia have been considered in a review by Gilman; [2] the overall reaction suggested is:

$$PbR_4 + 2e^- + NH_3 = PbR_3^- + RH + NH_2^-$$

Most studies of these systems have however been concerned primarily with the use of ions PbR_3^- in synthesis of unsymmetrical lead tetra-alkyls; the hydrocarbon products have not been investigated quantitatively, nor has solvolysis of the products been examined. Moreover it is not certain that only PbR_3^- ions are formed initially; Kraus and Sessions,[3] studying SnR_4 compounds, postulated reactions:

$$SnR_4 + e^- \longrightarrow SnR_3 + R^-$$

followed by

$$R^- + NH_3 \longrightarrow RH + NH_2^-$$

and

$$SnR_3 + e^- \longrightarrow SnR_3^-$$

If PbR_3 radicals are in fact formed then these may lose further alkyl groups, or disproportionate to lead and lead tetra-alkyls. It was therefore considered that studies of metal–ammonia reactions with trialkyl-lead halides should also be made, since the initial reaction would then be $PbR_3^+ + e^- = PbR_3$ and further products would be those originating from PbR_3 radicals.

In previous work,[1] only potassium was used; in the present work, sodium and lithium are found to yield different results from potassium, because of differences in the solubilities of the amides in liquid ammonia.

Experimental

Metal–ammonia solutions were handled, and gaseous and volatile products were analysed, in a vacuum.[1] Tetramethyl-lead and trimethyl-lead chloride were prepared by conventional methods and analysed. The lead compound and alkali metal in liquid ammonia were allowed to react in a sealed tube until the blue colour disappeared. At the usual temperature of

[1] Hazlehurst, Holliday, and Pass, *J.*, 1956, 4653.
[2] Gilman, *Chem. Rev.*, 1954, **54**, 114.
[3] Kraus and Sessions, *J. Amer. Chem. Soc.*, 1925, **47**, 2361.

reaction, −78°, tetramethyl-lead was insoluble, and reaction was slow; trimethyl-lead chloride was soluble at this temperature, so reaction was much faster. The solutions continued to evolve hydrocarbon after disappearance of colour; this part of the reaction was completed by refluxing under a cold finger (−78°). Volatile products (including any tetramethyl-lead) and solvent were then removed, and the solid residue analysed for lead (as chromate), potassium if present (as potassium tetraphenylboron), and alkalinity (corresponding to amide content [1]). It was not found possible to determine tetramethyl-lead, whether unchanged or formed as a product.

Results.—These are given in Tables 1 and 2; only results for complete experiments carried out under reproducible conditions are quoted. The experiments are numbered for convenience in discussion; units are mmoles unless otherwise stated. Hydrogen, "initial" methane, and ethane were evolved before the colour vanished; "final" methane was that evolved on subsequent ammonolysis, and the amide and lead readings were taken on the solid residues.

TABLE 1. *Experiments with tetramethyl-lead at* −78°.

Expt. no.	1	2	3	4	5	6	7
$PbMe_4$ added	2·74	1·60	1·81	2·14	1·28	2·28	2·30
Metal	K	K	K (at −33°)	Na	Na	Li	Li
Amt. added	2·91	3·77	2·78	2·57	3·88	3·04	2·40
Products: H_2	—	0·34	—	—	0·64	—	—
CH_4 (initial)	1·26	1·41	1·02	1·09	1·10	1·40	1·05
C_2H_6	0·14	0·08	0·15	0·14	0·12	0·11	0·11
CH_4 (Final)	4·70	4·55	3·94	1·38	1·32	1·32	1·37
NH_2^-	2·72	3·50	2·45	2·73	3·72	2·75	2·30
Pb	1·61	1·51	1·31	0·69	0·63	0·74	0·65
Time (hr.)	4	100	1·3	23	—	6	6

TABLE 2. *Experiments with trimethyl-lead chloride (at* −78°).

Expt. no.	8	9	10	11	12	13
Me_3PbCl added	0·40	0·20	0·21	0·47	0·45	0·20
Metal	K	K	K	K	Li	Li
Amt. added	0·79	0·38	0·51	2·93	0·98	0·29
Products: H_2	—	—	—	0·83	—	—
CH_4 (initial)	0·16	0·11	0·20	0·49	0·41	0·17
C_2H_6	—	—	—	—	—	—
CH_4 (final)	0·69	0·18	0·29	0·93	0·14	0·07
NH_2^-	0·44	0·17	0·21	2·37	0·51	0·23
Pb	0·29	0·12	0·15	0·43	0·25	0·09
Time (hr.)	0·16	0·16	0·16	164	0·25	0·25

DISCUSSION

The results for the potassium–tetramethyl-lead reactions suggest that the reaction ratio is 2 : 1; when potassium in excess is added (expt. 2), hydrogen is evolved, the amount indicating that the excess has reacted thus:

$$K + NH_3 = KNH_2 + \tfrac{1}{2}H_2$$

It is then reasonable to postulate that the first step in the reaction is

$$PbMe_4 + e^- \longrightarrow PbMe_3^- + Me \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

followed by

$$Me + e^- \longrightarrow Me^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$Me^- + NH_3 \longrightarrow MeH + NH_2^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

or

$$Me + Me \longrightarrow C_2H_6 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

In agreement with this scheme, the approximate relation [Initial $CH_4 + 2 \times C_2H_6$] = Pb holds for each experiment. The production of ethane would not be expected if reaction (1) were written

$$PbMe_4 + e^- \longrightarrow PbMe_3 + Me^-$$

Moreover, in expt. 2, where the initial electron concentration is high, the ratio C_2H_6/initial CH_4 falls, as is to be expected since high electron concentration will favour reaction (2) at the expense of (4). Increase of temperature (expt. 3) causes increased solubility of

tetramethyl-lead; there is a small increase in the C_2H_6/initial CH_4 ratio here, perhaps because of the greater extent of reaction (1).

On the above hypothesis, only one methyl radical is removed by electron attack, and the ion $PbMe_3^-$ remains in solution. Hence there is the possibility that three more methyl groups can be removed by solvent attack, and it appears that this does occur, since the relation [Final CH_4] = [3 × initial CH_4 + 6 × C_2H_6] holds in each experiment, even when excess of potassium is present. The solvolysis can be written stepwise thus:

$$PbMe_3^- + NH_3 \longrightarrow PbMe_2{\cdot}NH_2^- + CH_4 \quad . . . . . (5)$$

$$PbMe_2{\cdot}NH_2^- + NH_3 \longrightarrow PbMe(NH_2)_2^- + CH_4 \quad . . . . . (6)$$

$$PbMe(NH_2)_2^- + NH_3 \longrightarrow Pb(NH_2)_3^- + CH_4 \quad . . . . . (7)$$

$$Pb(NH_2)_3^- \longrightarrow PbNH + NH_3 + NH_2^- \quad . . . . . (8)$$

Evidence for the intermediate steps (5) and (6) is considered below; reactions (5), (6), and (7) together yield the observed amount of methane. The final reaction (8) is postulated because (*a*) the residue obtained was an orange solid, with a tendency to decompose explosively (characteristic of lead imide), and (*b*) formation of a further equivalent of amide ion is required to explain the observed approximate equality between added metal and amide ion produced.

When sodium or lithium is used instead of potassium (expts. 4—7), the total amount of methane (relative to the amount of metal added) is reduced, as is also the amount of residual lead. The ratio final CH_4/initial CH_4 is also decreased. The results of expt. 5, in which hydrogen is produced by the excess of sodium, suggest that the reaction ratio Na : $PbMe_4$ is 2 : 1, as with potassium. If this is true in the other experiments also, then it can be assumed that reactions (1)—(4) occur as with potassium, yielding methane and ethane; this assumption is supported by the observed equality Na(or Li) = 2[Initial CH_4 + C_2H_6]. If the first solvolysis (5) now follows, it alone yields sufficient final methane since it is seen that Final CH_4 = Initial CH_4 + C_2H_6 = $PbMe_3^-$. The product of reaction (5), $PbMe_2{\cdot}NH_2^-$, instead of undergoing further solvolysis, reacts with sodium (or lithium) ions, thus:

$$PbMe_2{\cdot}NH_2^- + Na^+ \longrightarrow PbMe_2 + NaNH_2 \quad . . . . . (9)$$

since the amides of sodium and lithium are insoluble in liquid ammonia at −78°. The dimethyl-lead may then remain until the temperature is raised to remove the last traces of solvent, then disproportionating:

$$2PbMe_2 \longrightarrow Pb + PbMe_4 \quad . . . . . (10)$$

and the tetramethyl-lead passes off as a volatile product, so that, as observed, the residual lead is only half that expected if solvolysis had been complete.

In the reactions of potassium with trimethyl-lead chloride (Table 2), the first step must be

$$Me_3PbCl + K \longrightarrow PbMe_3 + KCl \quad . . . . . (11)$$

and it might then be expected that the next would be:

$$PbMe_3 + e^- \longrightarrow PbMe_3^- \quad . . . . . (12)$$

and that this would be followed by the solvolysis (5)—(8), so that methane would only appear after the solution became colourless, if excess of trimethyl-lead chloride were used. In fact, some methane, but no ethane, appears before this stage; the amount is rather variable, being greater if more potassium is present. To explain this, we may postulate that the $PbMe_3$ radical initially formed can react in three possible ways:

$$(I)\ PbMe_3 + 3K + 3NH_3 = Pb + 3KNH_2 + 3CH_4$$

$$(II)\ PbMe_3 + K + 2NH_3 = PbNH + KNH_2 + 3CH_4$$

$$(III)\ PbMe_3 = 0{\cdot}75PbMe_4 + 0{\cdot}25Pb$$

In equation (I), the methane is put equal to the initial methane found, and the equation used to calculate how much potassium is required and how much lead and amide are produced. The remaining potassium is now assumed to react as in equation (II), and used to calculate how much more lead (imide), amide, and methane are produced from it. Subtraction of the lead formed in (I) and (II) from that available as $PbMe_3$ originally gives a quantity of the latter to react as in equation (III), yielding more residual lead. From the three equations therefore, calculated amounts of residual lead, amide, and final methane (from II) can be compared with the amounts actually found; this is done in Table 3, for

TABLE 3.

Experiment	8	9	10	11	12
Final CH_4: calc.	0·69	0·21	0·30	0·93	0·12
found	0·69	0·18	0·29	0·93	0·14
Residual Pb: calc.	0·31	0·11	0·18	0·47	0·25
found	0·29	0·12	0·15	0·43	0·25
Residual NH_2^-: calc.	0·39	0·18	0·30	2·46	0·53
found	0·44	0·17	0·21	2·37	0·51

expts. 8—11. (In expt. 11, with excess of potassium, the observed amount of hydrogen is used to calculate potassium used and amide produced according to the equation $K + HN_3 = KNH_2 + \frac{1}{2}H_2$.) The Table indicates that it is reasonable to accept the equations; the mechanisms must then be considered. The methane of equation (I) must be attributed to removal of methyl *ions* by electron attack on trimethyl-lead, thus:

$$\left.\begin{aligned} PbMe_3 + e^- &\longrightarrow PbMe_2 + Me^- \\ PbMe_2 + e^- &\longrightarrow PbMe + Me^- \\ PbMe + e^- &\longrightarrow Pb + Me^- \\ 3Me^- + 3NH_3 &\longrightarrow 3MeH + 3NH_2^- \end{aligned}\right\} \quad \ldots\ldots\ldots \quad (13)$$

This is clearly different from reaction (1) in which a methyl *radical* is formed; the total absence of ethane seems to preclude this reaction. The reason for the difference may lie in the different conditions; reaction (1) was operative where a small concentration of $PbMe_4$ was present, reacting slowly; here, a much larger concentration of $PbMe_3$ is reacting rapidly. Nevertheless, not all the $PbMe_3$ reacts as in (13); some must form the ion $PbMe_3^-$ by reaction (12), and this ion, in refluxing ammonia, undergoes complete solvolysis (5)—(8); hence the overall reaction given by equation (II). In the absence of excess of potassium, some $PbMe_3$ escapes attack by either of the above mechanisms, and finally disproportionates when the reaction products are heated to drive off solvent ammonia (equation III).

When lithium is used instead of potassium in the reaction with trimethyl-lead chloride (expts. 12 and 13), the relative amount of final methane is reduced. This is again attributed to cessation of solvolysis when reaction (5) is complete, the ion $PbMe_2 \cdot NH_2^-$ then reacting as in (9). Equation (II) now becomes $PbMe_3 + Li + NH_3 = PbMe_2 + KNH_2 + CH_4$ and calculated and experimental values can then be compared as before (expt. 12, Table 3).

The reaction mechanisms put forward in this paper are based upon stoicheiometric evidence only, and are therefore tentative. Kinetic measurements would be difficult but could test the validity of the reaction schemes proposed.

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DEPARTMENT OF INORGANIC AND PHYSICAL CHEMISTRY,
THE UNIVERSITY OF LIVERPOOL.

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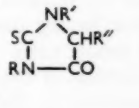
703. *Infrared Spectra of Some 2-Thiohydantoins: the Nature of the "Thioureide" Band.*

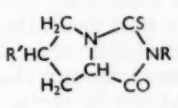
By D. T. Elmore.

The infrared spectra of a series of 2-thiohydantoins, including 1- and 3-monoalkyl and 1 : 3-dialkyl derivatives, have been measured over the range 2500—800 cm.$^{-1}$. The "thioureide" band, which is present in the spectra of compounds having no NH group, is not entirely due to a δNH vibration, although it is postulated that coupling between δNH and νCN modes may occur in suitable cases.

Randall, Fowler, Fuson, and Dangl [1] have attributed a strong band ("thioureide") in the infrared spectra of compounds containing the $>N-C(=S)-$ system to a νCN frequency modified by resonance of the type $>N-C(=S)- \longleftrightarrow N-C^{+}(-S^{-})-$. Bellamy [2] cautiously accepts this assignment. Chatt, Duncanson, and Venanzi,[3] however, have assigned this band to a major contribution of the canonical form $>N^{+}=C(-S^{-})-$ in the case of dithiocarbamates. The position of the band in the infrared spectrum is regarded as a manifestation of the bond order of the CN linkage. On the other hand, Mecke and Mecke [4] have studied the spectra of a number of cyclic thiolactams and thioureas and have concluded that the thioureide band is due to a δNH frequency comparable with the amide II band in primary and secondary amides and peptides. In addition, Hadži [5] has observed strong bands at 1523—1536 cm.$^{-1}$ in the spectra of thiobenzanilide, *N*-methyl(thiofuramide) and thiofuranilide, and these are attributed essentially to δNH modes. The evidence advanced includes (i) weakening or disappearance of the band after deuteration, (ii) a shift to lower frequencies in the liquid state [4] or in solution [5] compared with solid samples in pressed discs of potassium bromide, behaviour which is claimed to be more characteristic of a deformation than a stretching mode, and (iii) absence of the band in *N*-methyl(thiofuranilide).[5] In addition, Ramachandran, Epp, and McConnell,[6] who also attribute the thioureide band to a δNH frequency, report that it is absent from the spectra of 3-phenylpyrrolidino-(1′ : 2′-1 : 5)-2-thiohydantoin (II; R = Ph, R′ = H) and its 4′-hydroxy-derivative (II; R = Ph, R′ = OH). We notice, however, from the diagrams published by Hadži [5] and Ramachandran *et al.*[6] that compounds containing fully substituted nitrogen atoms absorb strongly at about 1450 cm.$^{-1}$. We believe that these bands, which are probably too strong to be confused with δCH modes, are modified thioureide bands as described below.



(I)



(II)

Several other compounds possessing the $>N-C(=S)-$ system, in which the nitrogen atom is tertiary, absorb strongly in the infrared region under consideration. Thus, thioureide bands are present in the spectra of (i) *NNN′N′*-tetramethylthiourea [7] at 1508 cm.$^{-1}$, (ii)

[1] Randall, Fowler, Fuson, and Dangl, "Infrared Determination of Organic Structures," D. van Nostrand Co. Inc., New York, 1949, p. 5.
[2] Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 1954, p. 294.
[3] Chatt, Duncanson, and Venanzi, *Suomen Kem.*, 1956, **29**, *B*, 75.
[4] Mecke and Mecke, *Chem. Ber.*, 1956, **89**, 343; Mecke, Mecke, and Lüttringhaus, *ibid.*, 1957, **90**, 975.
[5] Hadži, *J.*, 1957, 847.
[6] Ramachandran, Epp, and McConnell, *Analyt. Chem.*, 1955, **27**, 1734.
[7] Ettlinger, *J. Amer. Chem. Soc.*, 1950, **72**, 4699.

N-thioacetylpiperidine [8] at 1504 cm.$^{-1}$, (iii) salts and complexes of *NN*-dialkyldithiocarbamic acids [3,9] and methyl *NN*-dimethyldithiocarbamate [3] at 1480—1544 cm.$^{-1}$, and (iv) *NNN'N'*-tetra-alkylthiuram sulphides [9] and disulphides [3,9] at 1504—1514 cm.$^{-1}$. We have confirmed the observations on *NNN'N'*-tetramethylthiuram disulphide and *NNN'N'*-tetramethylthiourea. In addition, we have examined the infrared spectra of a number of 1 : 3-dialkyl-2-thiohydantoins, and in every case a strong thioureide band was present. Since the amide II band is absent from the spectra of all *NN*-dialkylamides so far examined,[10] it seems illogical to press the analogy of this band with the thioureide band too far.

Clow [11] determined the diamagnetic susceptibilities of a series of thioureas and concluded that the structure tended to the extreme form $(\rangle N)_2C{:}S$ as the degree of substitution of the nitrogen atoms was increased. Hence, if the thioureide band results from a νCN mode, it would be expected to shift to lower frequencies as the degree of substitution is increased and the contribution of $\overset{\delta+}{C}{-}N$ or $C{=}\overset{\delta+}{N}$ to the structure decreases. There are some examples in the literature. *NNN'*-Trimethylthiourea [7] absorbs at 1550 and *NNN'N'*-tetramethylthiourea [7] at 1508 cm.$^{-1}$; *N*-*n*-butyl(thioacetamide) [8] has a peak at 1542 and *N*-thioacetylpiperidine [8] at 1504 cm.$^{-1}$; *NN'*-dimethylthiuram disulphide [3] has a band at 1530 cm.$^{-1}$ with a shoulder at 1545 cm.$^{-1}$ while the corresponding peak for *NNN'N'*-tetramethylthiuram disulphide [3,9] is variously given as 1504 and 1514 cm.$^{-1}$; the ferric complexes of of *N*-ethyl- and *NN*-diethyl-dithiocarbamic acid [3] have bands at 1520 and 1496 cm.$^{-1}$ respectively. We now find that pyrrolidino(1′ : 2′-1 : 5)-2-thiohydantoin (II; R = R′ = H) has maximal absorption at 1508 and the 3-methyl derivative (II; R = Me, R′ = H) at 1458 cm.$^{-1}$. More generally in the thiohydantoin series, those compounds which are unsubstituted at $N_{(1)}$ and $N_{(3)}$ absorb at 1545—1562 cm.$^{-1}$; with a substituent at either $N_{(1)}$ or $N_{(3)}$ (I; R or R′ = H respectively), the band shifts to 1508—1539 cm.$^{-1}$, while with both positions blocked, the peak appears at 1458—1523 cm.$^{-1}$. Increase of size of substituent appears to enhance the size of shift.

Although Hadži [5] and Mecke and Mecke [4] claim that deuteration leads to disappearance of the thioureide band, we notice from their published spectra that a strong band usually appears at a slightly lower frequency. We have observed a corresponding shift following the deuteration of *N*-alkyl-2-thiohydantoins. 1-Methyl-2-thiohydantoin absorbs strongly at 1539, whereas the $N_{(3)}$-D-derivative has a peak at 1524 cm.$^{-1}$. Similarly, the peak at 1530 cm.$^{-1}$ in the spectrum of 3-ethyl-2-thiohydantoin is replaced by a peak at 1480 and shoulder at 1506 cm.$^{-1}$ after deuteration. In both cases, peaks near 1080 cm.$^{-1}$, which appear after deuteration, are probably due to δND modes.[5]

The above results lead us to the view that the thioureide band results from the coupling of a stretching frequency of a CN bond, modified by resonance as suggested by Randall *et al.*[1] or Chatt *et al.*,[3] with a δNH mode, the latter having the higher frequency. When the hydrogen is replaced by deuterium or an alkyl group, there is no possibility of coupling, and the band shifts to a lower frequency characteristic of the νCN mode alone. Hence, although the thioureide band may be partly dependent on the presence of an NH group for its position, it is not a diagnostic test.

In contrast to this assignment, Mecke and Mecke [4] and Hadži [5] have attributed bands at lower frequencies to νCN modes. While it is not possible at present to decide finally between these possibilities, some comments may be made concerning the interpretations due to these workers. (i) Hadži has examined only four thioamides, the spectra of which are very complex owing largely to the presence of aromatic and heterocyclic rings. (ii) The assignment of a band at 1330—1375 cm.$^{-1}$ to a νCN mode in these compounds may be

[8] Marvel, Radzitzky, and Brader, *J. Amer. Chem. Soc.*, 1955, **77**, 5997.
[9] Mann, *Trans. Inst. Rubber Ind.*, 1951, **27**, 232.
[10] Richards and Thompson, *J.*, 1947, 1248; Thompson, Brattain, Randall, and Rasmussen, "Chemistry of Penicillin," Princeton Univ. Press, Princeton, New Jersey, 1949, p. 388.
[11] Clow, *Trans. Faraday Soc.*, 1938, **34**, 457.

correct, but it would then be expected to arise from a C_{ar}–N bond,[12] as implied by Hadži.[5] It should, however, be pointed out that the νC=S frequency may appear here, as has been claimed in the case of thiocarbanilide.[13] Mecke and Mecke's [4] assignment of a band at ~1300 cm.$^{-1}$ in the spectra of cyclic thioamides and thioureas to a νCN mode has likewise been criticised recently by Lieber, Rao, Pillai, Ramachandran, and Hites,[14] who attribute this band to a νC=S vibration. It is also pertinent that Miyazawa, Shimanouchi, and Mizushima [15] concluded that a band at ~1300 cm.$^{-1}$ in the spectra of monosubstituted

Infrared spectra (cm.$^{-1}$) of 2-thiohydantoins in the solid state. s = *strong;* m = *moderate;* w = *weak;* sh = *shoulder;* c = *complex band.*

2-Thiohydantoin	5-Ethyl	5-*iso*Propyl	3-Ethyl	Deuterated 3-ethyl	3-Ethyl-1-methyl	1 : 3-Diethyl
1796 sh	1762 s *b*	1754 s *b*	1746 s *b*	2393 s *f*	1738 s *b*	1744 s *b*
1725 s *b*	1562 s *a*	1558 s *a*	1530 s *a*	1746 s *b*	1520 s *a*	1702 sh
1545 s *a*	1475 w *c*	1486 w	1456 sh *c*	1506 sh	1449 m } *h*	1514 s *a*
1430 m *c*	1416 s	1413 m	1435 m *c*	1480 s *a*	1435 m }	1465 m } *h*
1403 m	1396 sh	1395 m	1415 w	1450 sh	1400 s	1440 s }
1385 sh	1332 m	1353 w	1383 w	1424 s	1371 s	1422 s
1304 s	1271 m	1338 w	1351 s	1390 sh	1356 sh	1390 sh
1214 w	1251 w	1292 m	1311 s	1376 s	1308 s	1372 s
1174 s	1217 m	1270 w	1270 s	1349 s	1253 m	1353 s
1161 s	1186 s	1209 w	1207 m	1288 m	1223 s	1328 s
1046 w	1113 w	1190 m	1175 w	1247 s	1194 w	1285 s
980 w	1061 w	1176 s	1115 s	1206 m	1138 m	1242 s
967 w	980 w	1138 w	1049 m	1170 w	1116 w	1223 s
893 m	925 m	1100 w	980 w	1136 m	1098 w	1186 w
	872 w	1067 w	948 m	1116 s	1088 w	1142 m
5-Methyl		1032 w		1082 w *g*	1066 w	1122 s
1744 s *b*	5-*n*-Propyl	983 w	Deuterated	1042 s	992 m	1106 m
1553 s *a*	1744 s *b*	954 w	1-methyl	992 w	952 m	1074 m
1457 m *d*	1553 s *a*	926 w	~2400 mc *f*	974 w	883 m	1012 m
1416 s	1479 m *c*	887 w	1730 s *b*	960 w		981 w
1398 s	1458 w *e*		1524 s *a*	947 w		953 m
1315 s	1408 s	1-Methyl	1419 m	928 w		857 s
1184 s	1395 sh	1735 s *b*	1398 s	912 w		
1116 w	1333 m	1539 s *a*	1356 s	898 m	Pyrrolidino(1′ : 2′-1 : 5)-2-thiohydantoin	
1092 m	1324 m	1438 s *c*	1322 sh	850 w		
1044 m	1250 m	1400 s	1251 m	839 m	1749 s *b*	1172 m
969 w	1212 w	1349 s	1223 w		1709 m	1151 s
927 m	1179 s	1296 m	1189 m	1 : 3-Dimethyl	1508 s *a*	1108 w
825 m	1111 w	1249 s	1130 w }	1744 s *b*	1470 m *c*	1054 m
	1095 w	1228 w	1088 w } *i*	1633 w	1413 m	1018 w
	1037 w	1189 s	1075 w }	1523 s *a*	1340 m	989 m
	992 w	998 w	1068 w }	1462 m } *h*	1312 w	912 w
	959 m	968 w	1015 w	1449 m }	1279 w	907 w
	914 m	913 m	1005 w	1430 m	1255 m	891 w
	892 m		966 w	1390 s	1232 m	842 w
	857 w		939 m	1372 s		
			901 m	1353 sh	3-Methylpyrrolidino(1′ : 2′-1 : 5)-2-thiohydantoin	
			835 w	1328 s		
			815 s	1256 sh	1755 s *b*	1138 m
				1246 s	1458 s *a*	1090 w
				1182 w	1432 s *c*	1022 m
				1135 m	1334 s	989 m
				1099 m	1302 s	935 w
				1055 m	1247 w	914 w
				974 s	1173 w	896 w
				869 m		

a Thioureide, *b* νC=O, *c* δCH_3, *d* νC–CH_3, *e* δC–CH_3, *f* νND, *g* δND, h δCH modes, *i* one of these bands is probably δND

amides chiefly reflects δNH character. (iii) The argument [5] that bands at 1264 and 1280 cm.$^{-1}$ in the spectra of thiofuranilide and *N*-methylfuramide respectively are second νCN modes is weakened by the probability that at least one ν=C–O band attributable to

[12] Ref. 2, pp. 220—221.
[13] Jones, Kynaston, and Hales, *J.*, 1957, 614.
[14] Lieber, Rao, Pillai, Ramachandran, and Hites, *Canad. J. Chem.*, 1958, **36**, 801.
[15] Miyazawa, Shimanouchi, and Mizushima, *J. Chem. Phys.*, 1956, **24**, 408.

the furan ring will arise hereabouts. (iv) Hadži [5] has suggested that bands, which appear after deuteration at 1497 cm.$^{-1}$ with thiofuranilide and thiofuramide, and at 1468 cm.$^{-1}$ with thiobenzanilide, result from the interaction of a skeletal mode with either the δNH or νCN vibrations. Contribution from a δNH mode should be unimportant in a compound which is extensively deuterated; the alternative suggestion only differs from that of the present author by invoking a skeletal vibration, for which there seems no evidence.

It is of interest to record that *N*-ethylthiocarbamoylglycine ethyl ester cyclised to 3-ethyl-2-thiohydantoin in ethanolic ammonia at room temperature as well as in hot acid: this recalls the behaviour of *N*-thiocarbamoylglycine ethyl ester.[16] *N*-Benzoylthiocarbamoylglycine ethyl ester and *N*-ethyl-, *N*-phenyl-, and *N*-acetyl-thiocarbamoylglycylglycine ethyl ester were unaffected by ethanolic ammonia.

Experimental

Infrared spectra were obtained on a Grubb–Parsons double-beam spectrometer with rock-salt prism; specimens were prepared in potassium bromide discs. To obtain deuterated samples, the relevant compounds were kept in deuterium oxide at 100° for about 1 hr. The products crystallised with unchanged m. p. when the solutions were cooled.

3-Ethyl-2-thiohydantoin.—(*a*) Ethyl *iso*thiocyanate (4·2 g.) and glycine ethyl ester (from 7 g. of hydrochloride) were allowed to react in benzene (25 c.c.) at room temperature for 1 hr. Removal of solvent left *N*-ethylthiocarbamoylglycine ethyl ester as an oil. A mixture of the latter (1 g.), ethanol (2·5 c.c.), and 2N-hydrochloric acid (2·5 c.c.) was heated under reflux for 2 hr. Evaporation afforded the product (0·25 g.), which had m. p. 140—141°, unchanged after recrystallisation from water. (Jeffreys [17] records m. p. 144°.)

(*b*) A solution of the above oil (1 g.) in ethanolic ammonia (10 c.c.) was kept at room temperature for 2 hr. Evaporation yielded the product (0·15 g.), which had m. p. 140—141° alone and in admixture with the above specimen.

3-Ethyl-1-methyl-2-thiohydantoin.—This compound (68%) was prepared from ethyl *iso*thiocyanate and sarcosine ethyl ester by method (*a*) above. Recrystallised from benzene–light petroleum (b. p. 60—80°), it had m. p. 68·5—69·5°. (Jeffreys [18] records m. p. 67°.)

3-Methylpyrrolidino(1′ : 2′-1 : 5)-*2-thiohydantoin.*—DL-Proline (1·15 g.) and methyl *iso*thiocyanate (0·78 g.) were allowed to interact in 25% aqueous dioxan (40 c.c.) maintained at pH 9·5 by a pH-stat. The solution was evaporated to 10 c.c., adjusted to pH 1, and heated at 100° for 1 hr. After storage at 0°, the *thiohydantoin* (1·21 g.) crystallised. Recrystallised from benzene–light petroleum (b. p. 60—80°), it had m. p. 51·5—52·0° (Found: C, 49·2; H, 6·0; N, 16·3. $C_7H_{10}ON_2S$ requires C, 49·4; H, 5·9; N, 16·5%).

N-Ethylthiocarbamoylglycylglycine Ethyl Ester.—This *ester* (84%) was obtained from the reaction between ethyl *iso*thiocyanate and glycylglycine ethyl ester in chloroform. Recrystallised from chloroform–light petroleum (b. p. 40—60°), it had m. p. 97—98° (Found: C, 44·1; H, 7·2; N, 16·9. $C_9H_{17}O_3N_3S$ requires C, 43·7; H, 6·9; N, 17·0%).

N-Phenylthiocarbamoylglycylglycine Ethyl Ester.—Prepared in the same way, this *compound* (85%) had m. p. 140—141° after recrystallisation from chloroform–light petroleum (b. p. 40—60°) (Found: C, 52·8; H, 5·9; N, 14·6. $C_{13}H_{17}O_3N_3S$ requires C, 52·8; H, 5·8; N, 14·2%).

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Staveley Research Laboratories,
The University, Sheffield, 10. [*Received, April 18th,* 1958.]

[16] Elmore, Toseland, and Tyrrell, *J.*, 1955, 4288.
[17] Jeffreys, *J.*, 1954, 2221.
[18] *Idem, ibid.*, p. 389.

704. *The Synthesis of 5-Hydroxytryptamine (Serotonin) and Related Tryptamines.*

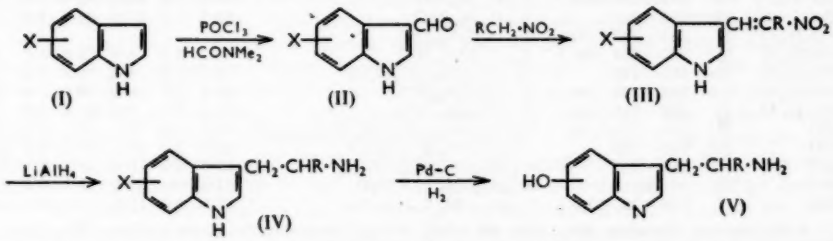
By Edwin H. P. Young.

A new route to 5-hydroxytryptamine (serotonin) and related substituted tryptamines is described. 3-2′-Nitrovinylindoles, readily prepared by the condensation of substituted indole-3-aldehydes and nitroparaffins, are reduced with lithium aluminium hydride to the corresponding substituted tryptamines. An improved method of preparation of the indole-3-aldehydes, which are now obtained in 85—95% yield, is also described.

5-Hydroxytryptamine (serotonin, enteramine) is of interest because of its isolation from blood platelets and from the gastrointestinal tract of animals and its numerous physiological actions.[1]

Several syntheses have been described; some [2] involve formation of the indole nucleus with the side chain carbon skeleton already present, whilst others [3] introduce the side chain into a ready-formed indole nucleus. Substituted tryptamines have recently [4] been obtained by opening the piperidine ring in 1 : 2 : 3 : 4-tetrahydro-1-oxo-β-carbolines.

The synthesis here described [5] starts from 5-benzyloxyindole (I; X = 5-$PhCH_2$·O) and follows the reaction sequence, depicted below, that has been frequently used to introduce the 2-aminoethyl side chain into medicinal compounds, *e.g.*, mescaline.[6] Several *Bz*-substituted indole-3-aldehydes have been prepared previously [7] in low yield by the Reimer–Tiemann reaction. By treating the indoles (I; X = 5-Cl, 5-MeO, 5-Me,



5-$PhCH_2$·O, 6-$PhCH_2$·O, and 6-MeO) with dimethylformamide and phosphorus oxychloride [8] the corresponding aldehydes have been obtained in high yield (85—95%) and purity. Although phosphorus oxychloride was the most convenient reagent it could be replaced by other phosphorus halides, and the excess of dimethylformamide by dioxan without appreciably affecting the yield or quality of product.

The aldehydes were condensed with nitroparaffins to give 3-2′-nitrovinylindoles (III; X and R, as in Table 1). Few condensations of this kind have been reported [9] and

[1] Page, *Physiol. Reviews*, 1954, **34**, 563; Erspamer, *Pharmacol. Reviews*, 1954, 425.

[2] Harley-Mason and Jackson, *J.*, 1954, 1165; Justoni and Pessina, *Il Farmaco, Ed. Sci.*, 1955, **10**, 356; Bernini, *Ann. Chim. appl.* (*Rome*), 1953, **43**, 559; Vejdělek and Tůma, *Československ. farm.*, 1955, **4**, 510.

[3] Hamlin and Fisher, *J. Amer. Chem. Soc.*, 1951, **73**, 5007; Speeter, Heinzelmann, and Weisblat, *ibid.*, p. 5515; Asero, Colò, Erspamer, and Vercellone, *Annalen*, 1952, **577**, 69; Ek and Witkop, *J. Amer. Chem. Soc.*, 1954, **76**, 5579; Speeter and Anthony, *ibid.*, p. 6208; Pietra, *Il Farmaco, Ed. Sci.*, 1958, **13**, 75.

[4] Abramovitch and Shapiro, *J.*, 1956, 4589.

[5] B.P. Appln. Nos. 4404—4407/1956.

[6] Slotta and Szyszka, *J. prakt. Chem.*, 1933, **137**, 347.

[7] Kermack, Perkin, and Robinson, *J.*, 1922, **121**, 1882; Blaikie and Perkin, *J.*, 1924, **125**, 296; Boyd and Robson, *Biochem. J.*, 1935, **29**, 555; Harvey and Robson, *J.*, 1938, 97; Marchant and Harvey, *J.*, 1951, 1808.

[8] Smith, *J.*, 1954, 3842.

[9] Seka, *Ber.*, 1924, **57**, 1868; Majima and Kotake, *Ber.*, 1925, **58**, 2037; Onda, Kawanishi, and Sasamoto, *J. Pharm. Soc. Japan*, 1956, **76**, 472.

TABLE 1. 3-2′-*Nitrovinylindoles* (III).

X	R	Reaction Temp.	Time (min.)	M. p.	Formula	Analyses Found, % C	H	N	Reqd., % C	H	N
H	H	95—98°	10	171—172° [a]	$C_{10}H_8O_2N_2$	64·4	4·7	14·9	63·8	4·25	14·9
H	Me	95—98	30	195—196	$C_{11}H_{10}O_2N_2$	65·4	5·2	13·7	65·35	4·95	13·9
H	Et	95—98	180	134—136	$C_{12}H_{12}O_2N_2$	66·6	5·5	13·2	66·7	5·55	13·0
5-Cl	H	95—100	10	186—187	$C_{10}H_7O_2N_2Cl$	54·1	3·5	12·5	53·9	3·1	12·6
5-MeO	Me	105—108	10	182—184	$C_{12}H_{12}O_3N_2$	61·6	5·4	11·7	62·1	5·2	12·1
5-Me	H	100	10	160—161	$C_{11}H_{10}O_2N_2$	65·9	5·3	13·6	65·35	4·95	13·9
5-Me	Me	100	10	184—187	$C_{12}H_{12}O_2N_2$	66·6	5·7	12·9	66·7	5·55	13·0
5-$PhCH_2$·O	H	95—98	30	181—182	$C_{17}H_{14}O_3N_2$	69·7	5·3	9·1	69·4	4·8	9·5
5-$PhCH_2$·O	Me	105—108	30	195—196	$C_{18}H_{16}O_3N_2$	70·0	5·2	9·6	70·1	5·2	9·1
5-$PhCH_2$·O	Et	110	45	175—176	$C_{19}H_{18}O_3N_2$	71·0	5·8	8·4	70·8	5·6	8·7
5-$PhCH_2$·O	C_7H_{15}	110—115 [b]	10	128	$C_{24}H_{28}O_3N_2$	73·9	7·1	—	73·5	7·1	—
6-$PhCH_2$·O	H	95—98	15	186—187	$C_{17}H_{14}O_3N_2$	69·5	4·9	9·5	69·9	4·8	9·6

[a] Ref. 24, m. p. 167—168° (decomp.); all other compounds are new. [b] Dimethylformamide was used as solvent.

TABLE 2. 3-2′-*Aminoethylindoles* (IV).

X	R	M. p.	Formula	Analyses Found, % C	H	N	Reqd., % C	H	N
H	H	249—250° [a] (dec.)	$C_{10}H_{13}N_2$,HCl	—	—	—	—	—	—
H	Me	215—217 [b]	$C_{11}H_{14}N_2$,HCl	62·9	7·1	13·1	62·7	7·1	13·3
H	Et	218—219 [b]	$C_{12}H_{16}N_2$,HCl	63·6	7·5	12·6	64·1	7·6	12·5
5-Cl	H	286—289 [c] (dec.)	$C_{10}H_{11}N_2Cl$,HCl	51·9	5·1	12·0	51·9	5·2	12·1
5-MeO	Me	220—221	$C_{12}H_{16}ON_2$,HCl	60·1	7·2	11·6	59·9	7·1	11·6
5-Me	H	289—291 (dec.)	$C_{11}H_{14}N_2$,HCl	62·8	6·9	13·4	62·7	7·1	13·3
5-Me	Me	256—257	$C_{12}H_{16}N_2$,HCl	63·8	7·7	12·5	64·1	7·6	12·5
5-$PhCH_2$·O	H	251—252 [d] (dec.)	$C_{17}H_{18}ON_2$,HCl	—	—	—	—	—	—
5-$PhCH_2$·O	Me	257—258 (dec.)	$C_{18}H_{20}ON_2$,HCl	68·2	6·6	8·8	68·2	6·6	8·8
5-$PhCH_2$·O	Me	181—182	$(C_{18}H_{20}ON_2)_2,C_4H_6O_4$	70·7	6·8	8·4	70·8	6·8	8·3
5-$PhCH_2$·O	Et	243—244 (dec.)	$C_{19}H_{22}ON_2$,HCl	69·4	7·1	8·2	69·0	7·0	8·5
6-$PhCH_2$·O	H	255—256 (dec.)	$C_{17}H_{18}ON_2$,HCl	67·4	6·5	9·2	67·4	6·3	9·3
5-HO	H	216—218 [d] (dec.)	$C_{10}H_{12}ON_2,C_4H_6ON_2,H_2SO_4,H_2O$	41·5	6·1	17·2	41·5	5·7	17·3
5-HO	Me	208—209	$C_{11}H_{14}ON_2,2C_4H_3O_7N_3$	42·8	3·0	17·3	42·6	3·1	17·3
5-HO	Et	183—184	$C_{12}H_{16}ON_2,2C_4H_3O_7N_3$	43·4	3·3	16·9	43·5	3·3	16·9
6-HO	H	192	$C_{10}H_{12}ON_2$,HCl,H_2O	51·6	6·0	12·7	52·1	6·5	12·1
6-HO	H	226—227 (dec.)	$C_{10}H_{12}ON_2,C_6H_3O_7N_3$	47·3	3·9	17·2	47·4	3·7	17·3

[a] Majima and Hoshino, *Ber.*, 1925, **28**, 2042. [b] Snyder and Katz, *J. Amer. Chem. Soc.*, 1947, **69**, 3140, report m. p. of bases. [c] Abramovitch, *J.*, 1956, 4593. [d] Ref. 3*b*.

in all cases reaction was slow. The condensation, however, takes place in 10—30 min. at about 100° with excess of the nitroparaffin as solvent and ammonium acetate as catalyst, high yields of almost pure product being obtained. Other catalysts and solvents were tried and, although 3-2′-nitrovinylindoles were obtained, the results were generally poor. There was no evidence of appreciable reaction between the nitro-olefins formed and the excess of nitroparaffin used.[10]

The nitro-olefins were reduced to the corresponding aminoethylindoles (IV; R and X, as in Table 2) by lithium aluminium hydride.[11] Catalytic reduction of nitro-olefins is known to present difficulties [12] and attempts to reduce the 3-2′-nitrovinylindoles by means of hydrogen and a platinum catalyst were unsuccessful.

The benzyloxy-3-2′-aminoethylindoles (IV; X = 5-$PhCH_2$·O; R = H, Me, or Et; X = 6-$PhCH_2$·O, R = H) were debenzylated by catalytic reduction, palladium on carbon or barium sulphate being used as catalyst.

The indoles were prepared by literature methods, except for 5-chloroindole. Attempts

[10] Heim, *Ber.*, 1911, **44**, 2016.

[11] Nystrom and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3738; Hamlin and Weston, *ibid.*, 1949, **71**, 2210; Ramirez and Burger, *ibid.*, 1950, **72**, 2781.

[12] Sonn and Schellenburg, *Ber.*, 1917, **50**, 1513; Skita and Keil, *Ber.*, 1932, **65**, 424; Kohler and Drake, *J. Amer. Chem. Soc.*, 1923, **45**, 1281.

to prepare this compound by Rydon and Long's method [13] were unsuccessful, as ethyl pyruvate *p*-chlorophenylhydrazone did not cyclise in acetic acid or ethanolic hydrogen chloride. Rydon and Tweddle [14] have since described the cyclisation of this compound with polyphosphoric acid. 5-Chloroindole was prepared as described by Uhle [15] for the 4-chloro-compound.

Experimental

5-Chloro-2-nitrophenylpyruvic Acid.—Potassium ethoxide [from potassium (8 g.) and ethanol (60 c.c.)] and anhydrous ether (300 c.c.) were treated dropwise, with stirring, with diethyl oxalate (29·2 c.c.). 5-Chloro-2-nitrotoluene (34·3 g.) was added gradually and the mixture gently refluxed for 3 hr., then cooled, and the potassium salt washed with ether. The dry salt (59 g.) was shaken with water (400 c.c.) at room temperature for 4 hr. and the solution then filtered. The filtrate was acidified (concentrated hydrochloric acid) and the *pyruvic acid* dried [37 g.; m. p. 180—182° (decomp.)]. The m. p. was not raised by crystallization from water (Found: C, 41·8; H, 1·8; N, 5·7. $C_9H_6O_5NCl,H_2O$ requires C, 41·3; H, 3·1; N, 5·35%).

5-Chloroindole-2-carboxylic Acid.—5-Chloro-2-nitropyruvic acid (10 g.) in ammonia (50 c.c.; *d* 0·88)–water (150 c.c.) was warmed (steam-bath) and a hot solution of ferrous sulphate ($FeSO_4,7H_2O$, 80 g.) in water (250 c.c.) added rapidly. The mixture was heated (steam-bath) for 1 hr. and then boiled for ½ hr. The iron residues were removed by filtration and washed with hot ammonia solution (5%; 50 c.c.). The hot filtrates were acidified (Congo Red) with concentrated hydrochloric acid and cooled to room temperature. The white solid was washed with a little cold water and dried (5·2 g.). 5-Chloroindole-2-carboxylic acid crystallized from aqueous ethanol in micro-needles, m. p. 291—292° (decomp.) (Found: C, 54·8; H, 2·9; N, 7·3. Calc. for $C_9H_6O_2NCl$: C, 55·1; H, 3·1; N, 7·2%).

5-Chloroindole.—5-Chloroindole-2-carboxylic acid (4·5 g.) was heated to 290° (bath temp.) until the solid began to fuse; the bath temperature was then reduced to 250—260° and kept there until evolution of carbon dioxide ceased (*ca.* 10 min.). The residue was distilled. Crystallization from light petroleum (25 c.c.; b. p. 80—100°) gave plates, m. p. 72—73° (1·48 g.) (Found: C, 63·4; H, 3·9; N, 8·9. Calc. for C_8H_6NCl: C, 63·3; H, 3·95; N, 9·2%).

5-Benzyloxyindole-3-aldehyde.—Phosphorus oxychloride (10 c.c.) was added dropwise, with stirring, at 10—20° to dimethylformamide (35 c.c.). A solution of 5-benzyloxyindole (22·3 g.) in dimethylformamide (25 c.c.) was then added gradually at 20—30°. The solution was then kept at 35—37° for 45 min. and finally poured into stirred ice (100 g.) and water (100 c.c.). Sodium hydroxide (19 g.) in water (100 c.c.) was added during ½ hr. at 20—30°, the rate of addition being such that when *ca.* 3/4 of the sodium hydroxide solution had been added the mixture was at pH 6. The remainder was then added at once. Water (200 c.c.) was added and the mixture boiled for 3 min. The *aldehyde* was washed with cold water (5 × 50 c.c.) and dried at 80° (21·6 g.). Crystallization from ethanol gave pale fawn needles, m. p. 237—238° (Found: C, 75·7; H, 5·3; N, 5·1. $C_{16}H_{13}O_2N$ requires C, 76·5; H, 5·2; N, 5·6%). Similarly the following indole-3-aldehydes were obtained: *5-chloro-*, m. p. 215—216° (93%) (Found: C, 60·1; H, 3·1; N, 8·0. C_9H_6ONCl requires C, 60·2; H, 3·3; N, 7·8%); 5-methoxy-, m. p. 181—182° (94%); 6-methoxy-, m. p. 187—189° (83%); 5-methyl-, m. p. 148—149° (92%).

6-Benzyloxyindole-3-aldehyde.—(*a*) By using 6-benzyloxyindole instead of the 5-compound in the above preparation, *6-benzyloxyindole-3-aldehyde* was obtained in 90% yield; it formed needles, m. p. 215—216° from 2-ethoxyethanol (Found: C, 76·3; H, 5·5; N, 5·5. $C_{16}H_{13}O_2N$ requires C, 76·5; H, 5·2; N, 5·6%). (*b*) Phosphorus tribromide (5 c.c.) was added to stirred dimethylformamide (20 c.c.) at 10—20°. A solution of 6-benzyloxyindole (5 g.) in dimethylformamide (10 c.c.) was added gradually at 20—30°. The experiment was completed as described above for 5-benzyloxyindole-3-aldehyde, 4·6 g. of product, m. p. 211—212°, being obtained. The m. p. was raised by crystallization from 2-ethoxyethanol to 215—216°. (*c*) Phosphorus pentachloride (2 g.) was used in place of the tribromide with 6-benzyloxyindole (1·5 g.) in dimethylformamide (5 c.c.). The aldehyde (1·2 g., m. p. 209—211°) was again obtained. (*d*) Phosphorus oxychloride (5 c.c.) was added at 10—20° to stirred dimethylformamide (5 c.c.)–dioxan (20 c.c.). 6-Benzyloxyindole (5 g.) in dioxan (10 c.c.) was added gradually

[13] Rydon and Long, *Nature*, 1949, **164**, 575.
[14] Rydon and Tweddle, *J.*, 1955, 3499.
[15] Uhle, *J. Amer. Chem. Soc.*, 1949, **71**, 761.

at 20—30°, and the mixture worked up as before. The product (4·9 g.; m. p. 208—209°) was purified by crystallization from 2-ethoxyethanol; it then had m. p. 215—216°.

The following experiments are typical of the methods employed to obtain the compounds described in Tables 1 and 2.

5-Benzyloxy-3-2′-nitrovinylindole.—5-Benzyloxyindole-3-aldehyde (4·4 g.), nitromethane (25 c.c.), and ammonium acetate (1 g.) were heated gently under reflux for ½ hr. On cooling, dark ruby prisms slowly separated (3·4 g. which crystallized from benzene or methanol as red prisms,

3-2′-Methyl-2′-nitrovinylindole.—(*a*) Indole-3-aldehyde hydrate (5 g.), nitroethane (10 c.c.), and ammonium acetate (1 g.) were heated on the steam-bath with occasional shaking for ½ hr. On cooling the crystals were collected, washed with hot water (2 × 50 c.c.), and crystallized from methanol; the product (3·1 g., m. p. 195—196°) was then obtained as yellow prisms. (*b*) Replacing ammonium acetate by butylamine (0·25 c.c.) and heating the mixture on the steam-bath for 1 hr. gave 3-2′-methyl-2′-nitrovinylindole which after crystallization from methanol had m. p. 195—196°, not altered on admixture with a sample made by use of ammonium acetate.

5-Benzyloxytryptamine Hydrochloride.—Lithium aluminium hydride (5 g.) was added to ether (250 c.c.) in the flask of a Soxhlet extractor. Finely ground 5-benzyloxy-3-2′-nitrovinylindole (3 g.) was then extracted from the thimble with ether for 6 hr. The product was cooled, and water (30 c.c.) added dropwise to decompose the excess of lithium aluminium hydride and the addition complex. The solid was filtered off and washed with ether (2 × 25 c.c.), and the ethereal solution dried (KOH) and then saturated with dry hydrogen chloride. The hydrochloride was collected and washed with ether; it (2·7 g.) had m. p. 251—252° (decomp.).

6-Benzyloxytryptamine Hydrochloride.—(*a*) This *hydrochloride* was prepared as described for the 5-compound; it crystallized from methanol–ethyl acetate in prisms (2·1 g.), m. p. 255—256° (decomp.). (*b*) 6-Benzyloxy-3-2′-nitrovinylindole (4 g.) in tetrahydrofuran (50 c.c.) was added during 15 min. to a stirred suspension of lithium aluminium hydride (4 g.) in tetrahydrofuran (150 c.c.). The mixture was stirred for a further 30 min. and allowed to cool. Water (20 c.c.) was cautiously added and the tetrahydrofuran solution was then filtered. The residue was washed with tetrahydrofuran (20 c.c.) and the combined filtrates were evaporated. The residual 6-benzyloxytryptamine was dissolved in ether and the solution saturated with hydrogen chloride, giving the hydrochloride [2·4 g.; m. p. and mixed m. p. with sample (*a*) 254—256° (decomp.)].

5-Hydroxytryptamine.—5-Benzyloxytryptamine hydrochloride (10 g.) was suspended in methanol (150 c.c.) and shaken in an atmosphere of hydrogen in the presence of palladium–carbon (10%; 2 g.) until adsorption of hydrogen stopped. The methanolic solution was filtered and the solvent evaporated *in vacuo*. The residue was dissolved in hot dilute sulphuric acid (2 c.c. of concentrated acid + 20 c.c. of water). Creatinine (4 g.) was added and the hot solution was filtered. The residue was washed with water (5 c.c.) and the combined filtrates were treated with acetone (150 c.c.). After 1 hr. the solid was collected and washed with acetone (20 c.c.) containing a few drops of water. The 5-hydroxytryptamine–creatinine sulphate complex (serotonin) (6·6 g.) had m. p. 216—218° (Found: C, 41·5; H, 6·1; N, 17·2; S, 7·9. Calc. for $C_{14}H_{19}O_2N_5,H_2SO_4,H_2O$: C, 41·5; H, 5·7; N, 17·3; S, 7·9%).

Tryptamine.—3-2′-Nitrovinylindole (15 g.) in a Soxhlet thimble was extracted continuously with dry ether for 8 hr. The ethereal extract was returned to the extractor flask which contained ether (500 c.c.) and lithium aluminium hydride (15 g.). The mixture was cooled and the complex was decomposed by gradual addition of water (80 c.c.). The solid was filtered off and washed with ether (2 × 100 c.c.). The ethereal solution was dried (Na_2SO_4) and saturated with hydrogen chloride. The hydrochloride (12·7 g.) was collected and crystallized from methanol–ethyl acetate giving prisms, m. p. 249—250° (decomp.).

Imperial Chemical Industries Limited Pharmaceuticals Division,
Alderley Park, Macclesfield, Cheshire. [*Received, May 9th*, 1958.]

705. *New Intermediates and Dyes. Part VI.* The Chemistry of 2-n-Butylanthraquinone. Derived Dyes for Synthetic Fibres.*

By Arnold T. Peters, jun., and Arnold T. Peters.

Many derivatives of 2-*n*-butylanthraquinone have been prepared and orientated.

The nitro-group in 2-*n*-butyl-1-nitroanthraquinone has been replaced, to give a series of alkylamino- and arylamino-derivatives, which are dyes for cellulose acetate rayon, Nylon, and Terylene; apart from a slight bathochromic effect, especially on Nylon, the shades and fastness of the dyeings were only slightly affected by the butyl group.

Dinitration of 2-*n*-butylanthraquinone was investigated in detail; the derived 1 : 5- and 1 : 8-diamino- and -bismethylamino-quinones were compared with the bluer 1 : 4-disubstituted analogues, prepared from 1-amino- and 1-methylamino-4-bromo-2-*n*-butylanthraquinone, respectively.

This paper concerns 2-*n*-butylanthraquinone, particularly dyes obtained by the introduction of the group NHR into position 1.

During the cyclisation of pure 2-4′-*n*-butylbenzoylbenzoic acid to 2-*n*-butylanthraquinone, achieved in 74% yield, by Peters and Rowe's method,[1] the butyl group was eliminated to a small extent, *ca.* 4% of anthraquinone being isolated. In experiments with the *tert.*-butyl analogues, the 2-*tert.*-butylanthraquinone was accompanied by 4—5% of anthraquinone. Elimination of the butyl group occurred during cyclisation rather than in the Friedel–Crafts reactions. 2-4′-Methylbenzoylbenzoic acid, however, similarly gave 2-methylanthraquinone, and no anthraquinone. Elimination of an alkyl group is unusual in such reactions, though Fieser and Peters [2] record the elimination of the 4- and the 4′-methyl group during the pyrolysis–cyclisation of 4 : 4′-dimethyl-1 : 1′-dinaphthyl ketone, and Ipatieff and Carson [3] describe dealkylation of di-*tert.*-butylbenzene to *tert.*-butylbenzene by sulphuric acid at 15°.

In reactions with alkyl derivatives, rearrangement, migration, and disproportionation are well known; in the Friedel–Crafts reaction *sec.*-butylbenzene and phthalic anhydride gave only a resinous 2-4′-*sec.*-butylbenzoylbenzoic acid, and difficulties in the purification of 2-4′-*n*-butylbenzoylbenzoic acid may be due to slight isomerisation by aluminium chloride.

2-*n*-Butylanthraquinone was mononitrated by Moualim and Peters's method,[4] but appreciable dinitration occurred also; the use of nitric acid in 100% sulphuric acid at <35° gave 65% of 2-*n*-butyl-1-nitroanthraquinone, with negligible dinitration. This product was orientated on oxidation with acid dichromate to 1-nitroanthraquinone-2-carboxylic acid, identical with that prepared from 2-methyl-1-nitroanthraquinone. Further evidence of the α-position of the nitro-group was afforded by conversion of the compound by aqueous-alcoholic ammonia at 130° into 1-amino-2-*n*-butylanthraquinone, best prepared however by reduction with aqueous-alcoholic sodium sulphide.

The bright yellow 1-acetamido- and golden-yellow 1-benzamido-2-*n*-butylanthraquinone were purified by chromatography; the latter dyed cotton from an alkaline sodium dithionite vat a pale greenish-yellow.

1-Amino-2-*n*-butylanthraquinone was converted by the diazo-reaction into 2-*n*-butyl-1-chloroanthraquinone, identical with one of the products obtained by direct controlled chlorination of 2-*n*-butylanthraquinone by sulphuryl chloride in nitrobenzene; further,

* Part V, *J.*, 1957, 1525.

[1] Peters and Rowe, *J.*, 1945, 181.
[2] Fieser and Peters, *J. Amer. Chem. Soc.*, 1932, **54**, 3742.
[3] Ipatieff and Carson, *ibid.*, 1937, **59**, 1417.
[4] Moualim and Peters, *J.*, 1948, 1627.

the 1-chloro-derivative was reconverted into 1-amino-2-*n*-butylanthraquinone by acid hydrolysis of the derived 2-*n*-butyl-1-toluene-*p*-sulphonamidoanthraquinone.

Pure 2-*n*-butyl-1-nitroanthraquinone with the appropriate *n*-alkylamine in alcohol at 120—125° gave the deep bordeaux 2-butyl-1-methylamino-, -1-ethylamino-, -1-*n*-propylamino-, and -1-*n*-butylamino-anthraquinone in yields of 80—83%.

The orange 2-*n*-butyl-1 : 2′ : 2′-difluoroethylaminoanthraquinone was prepared from the nitro-compound in boiling dry pyridine, but better by heating it with 2 : 2-difluoroethylamine, sodium acetate, copper acetate, and alcohol at 140—150°. An analogous derivative could not be obtained from 2 : 2 : 2-trifluoroethylamine.

1-Amino-2-*n*-butylanthraquinone was mainly unchanged on attempted reaction with ethylene chlorohydrin at 125—130°, but the deep purple 2-*n*-butyl-1-2′-hydroxyethylaminoanthraquinone was obtained from the 1-nitro-derivative and alcoholic 2-hydroxyethylamine at 120—125°, or less readily in refluxing pyridine in presence of sodium acetate, copper acetate, and a trace of copper bronze. In these reactions, particularly in open reflux, the use of an excess of 2-hydroxyethylamine gave a considerable amount of 1-amino-2-*n*-butylanthraquinone, formed by decomposition of 2-hydroxyethylamine. As the 1-2′-hydroxyethylamino-derivative was strongly absorbed on alumina, the 1-amino-derivative was readily separated. Meltsner *et al.*[5] observed that when nitrobenzene was heated with 2-hydroxyethylamine and sodium carbonate, 12% of aniline was formed, the 2-hydroxyethylamine being partly decomposed to ammonia and acetaldehyde.

Refluxing at 1 atm. was effective in the interaction of *cyclo*hexylamine and 2-butyl-1-nitroanthraquinone, which in boiling pyridine afforded the dark red 1-*cyclo*hexylamino-2-*n*-butylanthraquinone; similarly, refluxing with benzylamine in presence of sodium acetate and copper acetate gave 90% of the bright red 1-benzylamino-derivative. The bordeaux 1-anilino-2-*n*-butylanthraquinone was obtained in 50% yield by use of refluxing aniline in presence of copper bronze.

Certain of the above 1-substituted 2-*n*-butylanthraquinones were tested as dyes and compared with the respective anthraquinone analogues. In general, introducing the *n*-butyl group reduced the rate of dyeing at ordinary dyeing temperatures on cellulose acetate rayon and Nylon; on Terylene, differences were slight. Apart from a slight bathochromic effect, especially on Nylon, the shades of all dyeings were similar to those shown by the analogues containing no butyl group. Fastness to sublimation, light, and burnt gas fumes was not improved by the presence of the butyl group, but fastness to washing was excellent on all three fibres, possibly owing to increased molecular size. The alkylamino-group was bathochromic in the order: anilino > 2-hydroxyethylamino > amino > 2 : 2-difluoroethylamino. With cellulose acetate rayon and Nylon, the rate of dyeing was of the order amino = 2-hydroxyethylamino > 2 : 2-difluoroethylamino > anilino; on Terylene, dyeings gave almost complete exhaustion of the dyebath.

Further evidence that the orientation of 1-amino-2-*n*-butylanthraquinone was correct was afforded by its monobromination, followed by replacement of the bromine by the amino-group. Thus, bromination in dry nitrobenzene at 95° yielded 60% of 1-amino-4-bromo-2-*n*-butylanthraquinone; the melting point, as with certain other anthraquinone derivatives, is not an absolute criterion of purity, and confirmatory analyses from successive crystallisations were carried out to ensure purity; chromatography was unsuccessful. The bromine atom was readily replaced, to give the deep violet 1 : 4-diamino-2-*n*-butylanthraquinone, which gave similar dyeings to those from 1 : 4-diaminoanthraquinone. The derived yellow diacetamido- and the golden-orange dibenzamido-compound were shown to be homogeneous by chromatography. 4-Bromo-2-*n*-butyl-1-methylaminoanthraquinone, obtained by bromination of 2-*n*-butyl-1-methylaminoanthraquinone, and alcoholic methylamine yielded the deep violet 1 : 4-bismethylamino-2-*n*-butylanthraquinone.

Dinitration of 2-*n*-butylanthraquinone was studied in detail, and chromatography and

[5] Meltsner, Wohlberg, and Kleiner, *J. Amer. Chem. Soc.*, 1935, **57**, 2554.

fractional crystallisation were employed in the separation of the dinitro- and the derived diamino-derivatives. Potassium nitrate and sulphuric acid at <40° afforded approximately 55·6% of 1 : 5- and 33·3% of 1 : 8-, with 5·8% of 1 : *x*-dinitro-compound, and 5·2% of 2-*n*-butyl-1-nitroanthraquinone (yields are based on relative amounts of pure products isolated). Reduction by aqueous-alcoholic sodium sulphide of the various fractions gave 1 : 5- and 1 : 8-diamino-2-*n*-butylanthraquinone, and the 1 : *x*-diamino-derivative was separated by chromatography into two diamines, which were probably the 1 : 6- and 1 : 7-compounds. Diacetylation and dibenzoylation of the 1 : 5-diamine, as expected, proceeded more readily than with the 1 : 8-diamine.

The reddish-brown 2-*n*-butyl-1 : 5- and -1 : 8-bismethylaminoanthraquinone were prepared from the respective dinitro-analogues by the usual procedure. When 2-*n*-butyl-1 : 5-dinitroanthraquinone was heated with freshly distilled 2-hydroxyethylamine at 135—140° in presence of sodium acetate and alcohol, and the products were chromatographed, the reddish-violet 1(or 5)-amino-2-*n*-butyl-5(or 1)-2′-hydroxyethylamino- and the magenta 2-butyl-1 : 5-di-2′-hydroxyethylaminoanthraquinone were isolated. Isolation of the monoamine parallels the reaction recorded with ethanolamine.

On cellulose acetate rayon, dyeings of the three diamino-2-*n*-butylanthraquinones showed the deep reddish-violet of the 1 : 4-diamine, the 1 : 5- and 1 : 8-diamines affording reddish-orange and orange-red shades, respectively. Replacement of the amino-group by methylamino showed a bathochromic effect in all cases, the 1 : 4-, 1 : 5-, and 1 : 8-derivatives giving blue, bluish-red, and reddish-violet shades, respectively.

Experimental

2-n-*Butylanthraquinone*.—Cyclisation [1] of pure 2-4′-*n*-butylbenzoylbenzoic acid (10 g.), m. p. 100°, gave 2-*n*-butylanthraquinone, cream needles, m. p. 90° (6·9 g., 74%). Fractional crystallisation of the cyclised product yielded anthraquinone, pale yellow needles, m. p. and mixed m. p. 286° (from acetic acid) (0·3 g., 4%). Fractionation of the product derived from pure 2-*n*-butylanthraquinone and 20% oleum at 90—95° for 1 hr. gave no anthraquinone; only unchanged product was isolated, but there was some charring and sulphonation.

Interaction of *sec.*-butylbenzene, b. p. 173°, with phthalic anhydride in carbon disulphide or *s*-tetrachloroethane, was investigated several times, but yielded only an alkali-soluble yellow glass. Treatment with 20% oleum at 95° afforded a dark resin, with sulphonated products.

2-n-*Butyl*-1-*nitroanthraquinone*.—(*a*) Nitration of 2-*n*-butylanthraquinone (13·2 g.) by Moualim and Peters's method [4] gave 2-*n*-butyl-1 : 5-dinitroanthraquinone (2·3 g.), pale yellow needles, m. p. 264—265° (Found: C, 60·95; H, 4·0; N, 8·0. Calc. for $C_{18}H_{14}O_6N_2$: C, 61·0; H, 4·0; N, 7·9%), and 2-*n*-butyl-1-nitroanthraquinone, pale yellow needles, m. p. 150° (9·4 g., 60·8%) (Found: C, 69·7; H, 4·9; N, 4·5. Calc. for $C_{18}H_{15}O_4N$: C, 69·9; H, 4·9; N, 4·5%). Reaction for 10—12 min. at >38° gave some unnitrated material and the 1-nitro-derivative (7·8 g.), with only a small amount of dinitro-derivative.

(*b*) 2-*n*-Butylanthraquinone (6·3 g., 1 mol.) in 100% sulphuric acid (25 ml.) was stirred at 20° during the addition of nitric acid (*d* 1·41; 2·3 g., 1·08 mols.) and 100% sulphuric acid (6 ml.) (30 min.) at <35°. After 75 minutes' stirring at room temperature addition to water gave a pale yellow solid (6·9 g.), m. p. 125—130°, and thence by crystallisation from acetic acid the 1-nitro-derivative (4·8 g., 65%), m. p. 150°.

Oxidation of 2-n-*Butyl*-1-*nitroanthraquinone*.—Sodium dichromate (3·2 g.) in water (4 ml.) was added during 30 min. to the 1-nitro-derivative (3·7 g.) and 75% aqueous sulphuric acid (8 ml.) at 50°. After 20 hours' stirring at 65°, cooling, and filtration, the solid product was washed with water and digested with 20% aqueous sodium hydroxide at 85—90° for 45 min.; the purple alkaline filtrate was acidified with dilute sulphuric acid, to yield a gelatinous brownish-yellow precipitate, m. p. 260—270°. Four crystallisations (charcoal) from ethanol afforded pale brownish-yellow leaflets (0·2 g.), m. p. 289—290°, not depressed on admixture with 1-nitroanthraquinone-2-carboxylic acid, m. p. 290°, prepared from 2-methyl-1-nitroanthraquinone.

XUM

1-*Amino*-2-n-*butylanthraquinone*.—The 1-nitro-derivative (7 g.), prepared by method (*b*), was reduced by aqueous-alcoholic sodium sulphide [4] to the amine, long red needles, m. p. 175—176° (lit.,[4] m. p. 172°). Conversion of the nitro- into the amino-compound was also effected by heating it with aqueous ammonia (*d* 0·88; 18 ml. per g.) at 130° for 4 hr. It gave a stable diazonium salt, precipitated by zinc chloride as the double salt from the hydrochloric acid solution.

The free amine dyed cellulose acetate rayon and Nylon orange and salmon-pink shades, respectively.

The acetyl derivative crystallised from acetic acid in yellow needles, m. p. 154° (lit.,[4] m. p. 140°); further crystallisations did not alter the m. p., but chromatography from benzene on alumina gave a main yellow zone yielding yellow needles (from ethanol), m. p. 197°, of the 1-acetamido-derivative (Found: C, 74·9; H, 6·1; N, 4·3. Calc. for $C_{20}H_{19}O_3N$: C, 74·75; H, 6·0; N, 4·4%). Heating the amine and benzoyl chloride in dry nitrobenzene at 140—145° for 45 min. and then removing nitrobenzene with steam afforded a solid which crystallised from alcohol in golden-yellow needles, m. p. 128—129°. Chromatography (benzene–alumina) yielded similar needles, m. p. 129°, of 1-*benzamido*-2-n-*butylanthraquinone* (Found: C, 78·1; H, 5·5; N, 3·7. $C_{25}H_{21}O_3N$ requires C, 78·3; H, 5·5; N, 3·65%).

2-n-*Butyl*-1-*chloroanthraquinone*.—(*a*) 1-Amino-2-*n*-butylanthraquinone (2 g., 1 mol.) was dissolved in hot acetic acid (24 ml.), and the solution cooled rapidly to room temperature and added gradually to sodium nitrite (0·55 g., 1·1 mols.) in concentrated sulphuric acid (4 ml.). After 10 min., the resulting solution was added slowly to a stirred hydrochloric acid solution of cuprous chloride (freshly prepared from 2·5 g. of hydrated copper sulphate) at room temperature. After 1 hr., the mixture was warmed at 60° until evolution of nitrogen had ceased, and the resulting solid was collected and crystallised from ethanol in pale orange-brown prisms, m. p. 95—98° (1·9 g., 88·8%). Chromatography (benzene–alumina) gave a main yellow zone which afforded pale cream prisms, m. p. 103—104° (from ethanol), of the 1-*chloro-derivative* (Found: C, 72·2; H, 5·2; Cl, 11·75. $C_{18}H_{15}O_2Cl$ requires C, 72·4; H, 5·1; Cl, 11·9%).

(*b*) 2-*n*-Butylanthraquinone (4 g.) in dry nitrobenzene (10 ml.) was refluxed on the steam-bath with sulphuryl chloride (4·2 g.) and iodine (0·4 g.), for periods varying from 5 to 15 hr. Nitrobenzene was removed with steam, and the resulting solid was fractionally crystallised from ethanol. The products, usually cream solids, were as follows: reaction time, 5 hr., m. p. 74° (Found: Cl, 4·15%) and m. p. 80° (Found: Cl, 4·5%); 7 hr., m. p. 90° (Cl, 7·5%); 10 hr., m. p. 95—97° (Cl, 13·4%) and m. p. 102° (Cl, 11·65%); 12 hr., m. p. 108° (Cl, 14·45%) and m. p. 68° (Cl, 12·4%). The purest sample was obtained after reaction for 9 hr., and chromatography from benzene on alumina gave a main yellow zone and thence (from ethanol) cream prisms (0·8 g.), m. p. 103—104° (Found: C, 72·1; H, 4·9; Cl, 11·6%), identical with the product formed by method (*a*).

2-n-*Butyl*-1-*toluene*-p-*sulphonamidoanthraquinone*.—2-*n*-Butyl-1-chloroanthraquinone (1·1 g.) was heated with toluene-*p*-sulphonamide (0·9 g.), fused potassium acetate (0·8 g.), and a crystal of cupric acetate in dry nitrobenzene (10 ml.) at 190° for 3 hr. Most (0·64 g.) of the product was isolated by addition of ethanol; removal of nitrobenzene with steam gave a further 0·2 g. Purification (benzene–alumina) gave a reddish-blue band, rapidly eluted, and a main orange-brown zone; extraction of the latter with ethanol and crystallisation from the same solvent gave brownish-orange needles, m. p. 157°, of the *toluene*-p-*sulphonamido-derivative* (0·51 g.) (Found: C, 68·95; H, 5·25; N, 3·1; S, 7·4. $C_{25}H_{23}O_4NS$ requires C, 69·2; H, 5·35; N, 3·2; S, 7·4%). Hydrolysis of this derivative (0·6 g.) with concentrated sulphuric acid (5 ml.) at 90° for 20 min. afforded 1-amino-2-*n*-butylanthraquinone (0·3 g.), m. p. and mixed m. p. 174—175°.

1-n-*Alkylamino*-2-n-*butylanthraquinones*.—2-*n*-Butyl-1-nitroanthraquinone (1 g.) was heated with the appropriate 33% alcoholic alkylamine (12 ml.) at 120—125° for 2 hr.; the products, purified by chromatography and crystallised from alcohol, were: 2-n-*butyl*-1-*methylamino*- (0·76 g., 80·2%), dark bordeaux needles with a metallic lustre, m. p. 68—69° (Found: C, 77·9; H, 6·5; N, 4·9. $C_{19}H_{19}O_2N$ requires C, 77·8; H, 6·5; N, 4·8%), -1-*ethylamino*- (0·8 g., 80%), red needles, m. p. 85—86° (Found: C, 78·2; H, 7·1; N, 4·6. $C_{20}H_{21}O_2N$ requires C, 78·1; H, 6·9; N, 4·6%), -1-n-*propylamino*- (0·85 g., 81·7%), deep bordeaux needles, m. p. 52—53° (Found: C, 78·7; H, 7·3; N, 4·4. $C_{21}H_{23}O_2N$ requires C, 78·5; H, 7·2; N, 4·4%), and -1-n-*butylamino*-*anthraquinone* (0·9 g., 83%), deep bordeaux needles, m. p. 51—52° (Found: C, 78·7; H, 7·5; N, 4·15. $C_{22}H_{25}O_2N$ requires C, 78·8; H, 7·5; N, 4·2%). The m. p.s of these derivatives were rather low for effective dyeing procedures.

2-n-*Butyl*-1-2′ : 2′-*difluoroethylaminoanthraquinone*.—(*a*) 2 : 2-Difluoroethylamine (0·8 g.) was added dropwise during 15 min. to a solution of 2-*n*-butyl-1-nitroanthraquinone (1·5 g.) in pure dry pyridine (17 ml.) at 100°, and the mixture then refluxed for 40 hr.; the blood-red mixture was concentrated to 12 ml., then added to water, and the solid (1·35 g.), m. p. 127—129°, was purified by chromatography (toluene–alumina). A small strongly adsorbed reddish-violet zone was noted above the principal reddish-orange zone; the former yielded unidentified reddish-orange prisms (0·04 g.), m. p. 112° (from ethanol) (Found: N, 4·1%), and the latter afforded pale reddish-orange needles (0·6 g.), m. p. 103—104° (alcohol) (Found: C, 69·9; H, 5·4; N, 4·2. $C_{20}H_{19}O_2NF_2$ requires C, 69·95; H, 5·6; N, 4·1%), of the *difluoro-derivative*.

(*b*) The 1-nitro-derivative (1·2 g.), 2 : 2-difluoroethylamine (1·5 g.), fused sodium acetate (1 g.), copper acetate (0·1 g.), and alcohol (10 ml.) at 140—150° for 20 hr. gave a dark reddish-orange product (1·15 g.). Dissolution in chlorobenzene and chromatography on alumina gave (i) (strongly adsorbed) dark orange irregular prisms (0·18 g.), m. p. 118—119° (Found: C, 69·85; H, 5·7; N, 7·25%), of unknown constitution, (ii) (less strongly absorbed) deep red needles (0·4 g.) of 1-amino-2-*n*-butylanthraquinone, m. p. and mixed m. p. 175—176°, and (iii) (eluted) orange needles (0·28 g.), m. p. 103—104° (from ethanol), identical with the product obtained by method (*a*) (Found: C, 70·2; H, 5·9; N, 4·0%).

Reaction with 2 : 2 : 2-*Trifluoroethylamine*.—This amine (2 g.) and 2-*n*-butyl-1-nitroanthraquinone (1 g.), in presence of sodium acetate (0·75 g.) and alcohol (3 ml.) at 140—150° for 15 hr. afforded, after chromatography, a *substance* (dark reddish-orange needles; 0·C8 g.), m. p. 144—146° (from ethanol) (Found: C, 66·45; H, 5·15; N, 8·25. $C_{20}H_{18}O_2NF_3$ requires C, 66·5; H, 5·0; N, 3·8%), of unknown constitution, and pale orange needles (0·67 g.), m. p. 145—146°, of unchanged nitro-compound (Found: C, 69·6; H, 4·7; N, 4·8%).

2-n-*Butyl*-1-2′-*hydroxyethylaminoanthraquinone*.—Interaction of 1-amino-2-*n*-butylanthraquinone with ethylene chlorohydrin in presence of sodium and copper acetates in a sealed tube at 125—130° for 3 hr. gave only a trace of bluish-red product, and the amine was mainly recovered. 2-*n*-Butyl-1-nitroanthraquinone (1 g.) and 33% v/v alcoholic 2-hydroxyethylamine at 120—125° for 2 hr. gave, after chromatography (toluene–alumina), red needles (0·2 g.), m. p. 175—176°, of 1-amino-2-*n*-butylanthraquinone; a strongly adsorbed small red zone gave bordeaux prisms (0·25 g.), m. p. 103—104° (from ethanol) (Found: C, 73·5; H, 6·8; N, 3·8. $C_{20}H_{21}O_3N$ requires C, 74·3; H, 6·55; N, 4·3%), of impure product. The use of 2-hydroxyethylamine (5 ml.) and ethanol (6 ml.), as above, again gave a little 1-amino-2-*n*-butylanthraquinone, but the principal dark red zone yielded deep purple prisms (0·4 g., 38%), m. p. 114° [from alcohol–light petroleum (b. p. 60—80°)], of 2-n-*butyl*-1-2′-*hydroxyethylaminoanthraquinone* (Found: C, 74·1; H, 6·4; N, 4·3%). The same product (0·32 g., 30·6%) and 1-amino-2-*n*-butylanthraquinone (0·22 g., 24·3%) were obtained by refluxing the 1-nitro-compound (1 g.) with pyridine (12 ml.) and freshly distilled ethanolamine (0·3 g.) in presence of sodium acetate (0·8 g.), copper acetate (0·1 g.), and a trace of copper bronze. 2-*n*-Butyl-1-2′-hydroxyethylaminoanthraquinone dyed cellulose acetate rayon, Nylon, and Terylene clear pink, bluish-pink, and pink shades, respectively, and all cases showed a slightly bluer shade than the corresponding dyeings from 1-2′-hydroxyethylanthraquinone.

2-n-*Butyl*-1-cyclo*hexylaminoanthraquinone*.—Refluxing 2-*n*-butyl-1-nitroanthraquinone (1 g.) with *cyclo*hexylamine (6 ml.) and dry pyridine (14 ml.) for 7 hr., then adding the mixture to dilute hydrochloric acid gave a resin which on prolonged storage *in vacuo* yielded a dark purple mass (0·78 g.), m. p. 70—75°; ether-extraction of the aqueous layer gave a dark red solid (0·24 g.), m. p. 75—77°. The products were combined and chromatographed (benzene–alumina) to yield a main bright bluish-red zone; extraction with ethanol, followed by crystallisation from light petroleum (b. p. 60—80°), gave dark red needles, m. p. 84—85°, of the 1-cyclo*hexylamino-derivative* (0·75 g., 64·1%) (Found: C, 79·6; H, 7·5; N, 3·7. $C_{24}H_{27}O_2N$ requires C, 79·8; H, 7·5; N, 3·9%).

1-*Benzylamino*-2-n-*butylanthraquinone*.—The 1-nitro-derivative (1 g.) was refluxed with benzylamine (10 ml.) in presence of sodium acetate (1 g.), copper acetate (0·2 g.), and a trace of copper bronze for 5 hr., and the red solution was added to water. Chromatography from toluene gave a small pale yellow band and a main orange-red zone; the latter afforded deep brownish-red needles (0·63 g., 52·5%), m. p. 172—173° (from ethanol), of the 1-*benzylamino-derivative* (Found: C, 81·0; H, 6·15; N, 3·8. $C_{25}H_{23}O_2N$ requires C, 81·3; H, 6·3; N, 3·8%).

1-*Anilino*-2-n-*butylanthraquinone*.—The 1-nitro-derivative (1 g.) was heated under reflux

with dry aniline (15 ml.) and a little copper bronze for 12 hr., and the filtered mixture added to dilute aqueous hydrochloric acid. The resulting resin did not solidify or crystallise. Chromatography (chlorobenzene–alumina) gave a principal deep purple band which on extraction with ethanol (yield 0·57 g.) and crystallisation from acetic acid and then light petroleum (b. p. 60—80°) yielded bordeaux prisms, m. p. 105—106°, of the *anilino-derivative* (Found: C, 81·0; H, 6·1; N, 3·9. $C_{24}H_{21}O_2N$ requires C, 81·1; H, 6·0; N, 3·9%). Cellulose acetate rayon, Nylon, and Terylene were dyed dull shades of pink, slightly bluer than those derived from 1-anilinoanthraquinone, but of somewhat weaker colouring power.

1-*Amino*-4-*bromo*-2-n-*butylanthraquinone*.—(*a*) Bromination of 1-amino-2-*n*-butylanthraquinone (2·8 g., 1 mol.) in dilute hydrochloric acid was incomplete.

(*b*) Bromine (2·9 g., 1·15 mols.) in dry nitrobenzene (8 ml.) was added during 30 min., with stirring, to 1-amino-2-*n*-butylanthraquinone (4·4 g., 1 mol.) and fused sodium acetate (1·5 g.) in dry nitrobenzene (40 ml.) at 8—10°. The mixture was kept at 95° for 90 min.; nitrobenzene was removed with steam, and the residue (5 g.; m. p. 141—143°) was fractionated from alcohol to give orange needles (3·3 g.) of the pure bromo-derivative, m. p. 151—152° (Found: C, 60·1; H, 4·4; N, 3·9; Br, 22·3. Calc. for $C_{18}H_{16}O_2NBr$: C, 60·4; H, 4·45; N, 3·9; Br, 22·3%); the mother-liquors gave a similar product (Found: Br, 18·2%) (lit.,[4] m. p. 148°).

4-*Bromo*-2-n-*butyl*-1-*methylaminoanthraquinone*.—The procedure of method (*b*) above gave red prismatic needles, m. p. 81—82° (from ethanol), of 4-*bromo*-2-n-*butyl*-1-*methylaminoanthraquinone* (2 g., 70·2%) (Found: C, 61·2; H, 4·7; N, 3·8; Br, 21·7. $C_{19}H_{18}O_2NBr$ requires C, 61·3; H, 4·9; N, 3·8; Br, 21·5%).

2-n-*Butyl*-1 : 4-*bismethylaminoanthraquinone*.—4-Bromo-2-*n*-butyl-1-methylaminoanthraquinone (1·5 g.), 33% alcoholic methylamine (25 ml.), sodium acetate (1·5 g.), and copper acetate (0·2 g.) in a sealed tube at 120—125° for 2 hr. gave a solid (1·1 g.), chromatographed in toluene on alumina to yield a readily eluted bluish-red zone and a main bright blue zone, strongly adsorbed; the latter afforded deep violet needles with a metallic lustre, m. p. 178—179° (from ethanol) (0·57 g., 44%), of the *bismethylamino-derivative* (Found: C, 74·4; H, 6·6; N, 8·2. $C_{26}H_{22}O_2N_2$ requires C, 74·5; H, 6·8; N, 8·7%).

1 : 4-*Diamino*-2-n-*butylanthraquinone*.—1-Amino-4-bromo-2-*n*-butylanthraquinone (1·5 g.), aqueous ammonia (*d* 0·88; 24 ml.), sodium acetate (2 g.), copper acetate (0·2 g.), and alcohol (12 ml.) at 120—125° for 2 hr. gave a solid, and thence by chromatography in toluene, a main intense reddish-violet band; the *diamine* crystallised from ethanol in deep violet needles, m. p. 211—212° (0·8 g., 65%) (Found: C, 73·2; H, 6·0; N, 9·3. $C_{18}H_{18}O_2N_2$ requires C, 73·5; H, 6·2; N, 9·5%). On cellulose acetate rayon, the reddish-violet shade was brighter and bluer than that derived from 1 : 4-diaminoanthraquinone; Nylon was dyed a bluish-violet shade, and Terylene a reddish-violet, similar to the dyeings from 1 : 4-diaminoanthraquinone.

Refluxing the diamine with acetic anhydride gave the *diacetamido-compound* which crystallised from benzene–light petroleum (b. p. 60—80°) in yellow needles, m. p. 233—234° (Found: C, 70·1; N, 5·7; N, 7·7. $C_{22}H_{22}O_4N_2$ requires C, 69·8; H, 5·9; N, 7·4%). The *dibenzamido-compound*, prepared by use of benzoyl chloride in nitrobenzene at 140°, crystallised from acetic acid in golden-orange needles, m. p. 251—252° (Found: C, 76·2; H, 5·2; N, 5·5. $C_{32}H_{26}O_4N_2$ requires C, 76·45; H, 5·2; N, 5·6%); chromatography in chlorobenzene showed it to be homogeneous.

Dinitration of 2-n-*Butylanthraquinone*.—Potassium nitrate (6·67 g., 2·2 mols.) was added to 2-*n*-butylanthraquinone (7·93 g., 1 mol.) in sulphuric acid (100 ml.) at <40° during 20 min., and the mixture kept at room temperature for 8 hr. The solid was collected in a sintered-glass funnel (acid liquor *A*) and extracted with boiling alcohol to give the insoluble 1 : 5-dinitro-compound (3·5 g.), pale yellow needles, m. p. 264—265° (from acetic acid) (Found: C, 60·9; H, 3·8; N, 7·8. Calc. for $C_{18}H_{14}O_6N_2$: C, 61·0; H, 4·0; N, 7·9%); the alcohol-soluble portion was chromatographed in toluene to yield (eluted) orange-yellow needles, m. p. 148°, of 2-*n*-butyl-1-nitroanthraquinone, and a yellow band (light-sensitive) which gave brownish-orange needles (0·5 g.), m. p. 176—177° (from ethanol), of pure 1 : 8-dinitro-derivative (Found: C, 60·8; H, 3·9; N, 7·9%); the product, m. p. 158° (ref. 4, p. 1630), was impure. The acid liquors *A* were added to water, and the solid (3·5 g.) extracted with boiling alcohol to yield insoluble 1 : 5-dinitro-derivative, m. p. 264°, and from the soluble portion a solid (*B*; 2·2 g.) which was purified by chromatography in toluene to yield (eluted) a little 1-nitro-derivative, m. p. 148° (Found: N, 4·35%), brownish-orange needles (0·4 g.), m. p. 176—177°, of the 1 : 8-dinitro-derivative, and unidentified products. The solid *B* (1 g.) was reduced by aqueous-alcoholic sodium sulphide

to give a solid (0·94 g.), whence chromatography in toluene yielded a little 1-amino-2-*n*-butylanthraquinone, m. p. and mixed m. p. 175—176°, which was eluted, and two bands which afforded the 1 : 8-diamine, m. p. and mixed m. p. 166°, and, more strongly adsorbed, orange-brown prisms (0·2 g.), m. p. 169—170° (from ethanol); the last product was rechromatographed, to give reddish-orange needles of a *substance*, m. p. 193—194° (Found: C, 73·4; H, 6·1; N, 9·3. $C_{18}H_{18}O_2N_2$ requires C, 73·5; H, 6·2; N, 9·5%), and a lower band which afforded yellowish-orange needles of a substance, m. p. 240—245° (Found: N, 9·5%); these were not orientated, but were possibly the 1 : 6- and 1 : 7-diamino-derivative.

1 : 5- *and* 1 : 8-*Diamino*-2-n-*butylanthraquinone*.—Reduction of the pure 1 : 5-dinitro-compound (1 g.) with aqueous-alcoholic sodium sulphide gave yellowish-orange needles (0·73 g., 88·5%), m. p. 160°, of the 1 : 5-diamine (Found: C, 73·5; H, 6·1; N, 9·4. Calc. for $C_{18}H_{18}O_2N_2$: C, 73·5; H, 6·2; N, 9·5%). 1 : 5-*Diacetamido*-, orange needles (from ethanol), m. p. 239—240° (Found: C, 69·5; H, 5·9; N, 7·3. $C_{22}H_{22}O_4N_2$ requires C, 69·8; H, 5·9; N, 7·4%), and 1 : 5-*dibenzamido*-2-n-*butylanthraquinone*, yellow needles (from ethanol), m. p. 237—238° (alcohol) (Found: C, 76·6; H, 5·1; N, 5·8. $C_{32}H_{26}O_4N_2$ requires C, 76·45; H, 5·2; N, 5·6%), were prepared from this.

2-*n*-Butyl-1 : 8-dinitroanthraquinone (1 g.) similarly gave the 1 : 8-diamine (0·76 g., 92%), which crystallised from ethanol in brownish-red needles, m. p. 166° (Found: C, 73·4; H, 6·1; N, 9·7%); chromatography confirmed its homogeneity; but a sample, m. p. 140° (cf. ref. 4), was impure, probably containing 1-amino-derivative from a nitro-derivative which had not been removed by chromatography. 1 : 8-*Diacetamido*-, pale yellow needles, m. p. 240—241° (from ethanol) (admixture with the 1 : 5-isomer gave m. p. 210—212°) (Found: C, 69·5; H, 6·1; N, 7·4%), and the 1 : 8-*diacetamido*-2-n-*butylanthraquinone*, bright yellow needles, m. p. 242—243° (from ethanol) (Found: C, 76·5; H, 5·2; N, 5·6%), were shown to be homogeneous by chromatography and further crystallisation.

2-n-*Butyl*-1 : 5-*bismethylaminoanthraquinone*.—The 1 : 5-dinitro-compound (0·9 g.), 33% alcoholic methylamine (24 ml.), and sodium acetate (0·8 g.) in a sealed tube at 135—140° for 8 hr. gave a bluish-red solid (0·88 g.); chromatography in chlorobenzene separated a main deep reddish-purple band and thence reddish-brown needles with an intense bronze lustre (0·38 g.), m. p. 142—143° (from ethanol) (Found: C, 74·4; H, 6·7; N, 8·55. $C_{20}H_{22}O_2N_2$ requires C, 74·5; H, 6·8; N, 8·7%).

2-n-*Butyl*-1 : 8-*bismethylaminoanthraquinone*.—Prepared as above, this *base* crystallised from ethanol in reddish-brown needles with a bronze lustre, m. p. 104—105° (Found: C, 74·3; H, 6·8; N, 8·5%).

2-n-*Butyl*-1 : 5-*di*-(2-*hydroxyethylamino*)*anthraquinone*.—The 1 : 5-dinitro-compound (0·9 g.), freshly distilled 2-hydroxyethylamine (10 ml.), ethanol (5 ml.), and sodium acetate (0·8 g.), as above, gave after chromatography in *o*-dichlorobenzene two main zones, which yielded reddish-violet needles with a bronze lustre (0·28 g.), m. p. 171—172° (from ethanol) (Found: C, 70·7; H, 6·5; N, 8·2. $C_{20}H_{22}O_3N_2$ requires C, 71·0; H, 6·55; N, 8·3%), of 1(or 5)-*amino*-2-n-*butyl*-5(or 1)-2′-*hydroxyethylaminoanthraquinone*, and (more strongly adsorbed) magenta needles (0·24 g.), m. p. 148—149° (from ethanol) (Found: C, 69·1; H, 6·9; N, 7·15. $C_{22}H_{24}O_4N_2$ requires C, 69·1; H, 6·85; N, 7·3%), of 2-n-*butyl*-1 : 5-*di*-(2-*hydroxyethylamino*)*anthraquinone*.

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CLOTHWORKERS' RESEARCH LABORATORY,
THE UNIVERSITY, LEEDS.

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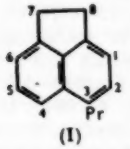
XUM

706. *Acenaphthene Series. Part VIII.* Propionyl and* n-*Propyl Derivatives of Acenaphthene and Naphthalic Anhydride.*

By David A. Wade and Arnold T. Peters.

3-*n*-Propylacenaphthene, obtained by Clemmensen reduction of 3-propionylacenaphthene, was converted into 4-*n*-propylnaphthalic anhydride and thence into 4-carboxynaphthalic anhydride. 1-Propionyl- and 3 : 4-dipropionyl-acenaphthene similarly afforded 1-*n*-propyl- and 3 : 4-di-*n*-propyl-acenaphthene. Direct *n*-propylation of acenaphthene was unsuccessful.

No propyl derivative of acenaphthene or naphthalic (naphthalene-1 : 8-dicarboxylic) anhydride is recorded. Dziewonski and Moszew [1] stated that propionyl chloride with acenaphthene in presence of aluminium chloride in carbon disulphide gave 3-propionylacenaphthene (I), m. p. 69—70°, and 3 : 4-dipropionylacenaphthene, m. p. 122—123°. Using nitrobenzene as solvent, Nightingale, Ungate, and French [2] obtained 3- and 1-propionylacenaphthene, m. p. 122—123°. We repeated the monopropionylation of acenaphthene and obtained identical products when we used either carbon disulphide or nitrobenzene, *viz.*, 3-, m. p. 65—66°, and 1-propionylacenaphthene, m. p. 119—120°, in yields of 54·6% and 16·3% (carbon disulphide), and 61·1 and 18·7% (nitrobenzene), respectively; this is analogous to the monoacetylation of acenaphthene by acetyl chloride in the Friedel–Crafts reaction.[3]



(I)

Using carbon disulphide as solvent, and 2 mols. of propionyl chloride, we converted acenaphthene into a dipropionylacenaphthene, m. p. 120—121°, which depressed the m. p. (119—120°) of 1-propionylacenaphthene to 96—108°; the dipropionyl derivative did not yield a solid picrate, whereas 1-propionylacenaphthene gave a picrate, m. p. 123—124°.

1- and 3-Propionylacenaphthene were oxidised by sodium dichromate in boiling acetic acid to give 2- and 4-propionylnaphthalic anhydride, respectively, converted into the corresponding naphthalimides. Clemmensen reduction of 1-propionylacenaphthene afforded 40% of 1-*n*-propylacenaphthene, which readily gave a crystalline picrate and a 1 : 3 : 5-trinitrobenzene derivative, and was oxidised to 2-*n*-propylnaphthalic anhydride. 3-Propionylacenaphthene similarly yielded 3-*n*-propylacenaphthene, oxidised by sodium dichromate to 4-*n*-propylnaphthalic anhydride and thence by permanganate to 4-carboxynaphthalic anhydride, identical with an authentic sample.[4]

Attempts at the interaction of *n*-propyl bromide and acenaphthene under a variety of conditions gave only recovered acenaphthene. Both 1- and 3-*n*-propylacenaphthene were recovered unchanged after treatment with anhydrous ferric chloride or aluminium chloride in boiling carbon disulphide; slight dealkylation was indicated by the isolation of traces of acenaphthene.

The dipropionylacenaphthene above was probably the 3 : 4-derivative; it was converted into 3 : 4-di-*n*-propylacenaphthene and 4 : 5-di-*n*-propylnaphthalic anhydride, the latter being oxidised by dilute nitric acid in a sealed tube at 170—180° for 24 hr. to give benzene-1 : 2 : 3 : 4-tetracarboxylic acid, identified as its tetramethyl ester.[4]

* Part VII, *J.*, 1952, 2730.

[1] Dziewonski and Moszew, *Bull. intern. Acad. polon.*, 1931, *A*, 242; 2*A*, 158; *Chem. Abs.*, 1931, **25**, 5674; 1932, **26**, 2191.
[2] Nightingale, Ungate, and French, *J. Amer. Chem. Soc.*, 1945, **67**, 1262.
[3] Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1939, **61**, 1272.
[4] Nursten and Peters, *J.*, 1950, 2389.

Experimental

1- *and* 3-*Propionylacenaphthene.*—Redistilled acenaphthene (90 g., 1 mol.), dry nitrobenzene (450 ml.), propionyl chloride (54 g., 1 mol.), and anhydrous aluminium chloride (84 g., 1·08 mols.) were stirred at 0—5°. The mixture was allowed to attain room temperature, and after 12 hr. the complex was decomposed with dilute hydrochloric acid, nitrobenzene was removed with steam, and the residue extracted with chloroform; the dried extract, after removal of solvent, gave a solid which on extraction with ether and cooling, yielded a pale brown solid. Crystallisation from ethanol (charcoal) afforded fine colourless needles, m. p. 119—120°, of 1-propionylacenaphthene (23 g., 18·7%) (Found: C, 85·4; H, 6·6. Calc. for $C_{15}H_{14}O$: C, 85·7; H, 6·7%). The ether mother-liquors were evaporated to dryness; the residue crystallised from ethanol (charcoal) in pale buff needles, m. p. 65—66°, of 3-propionylacenaphthene (75 g., 61·1%) (Found: C, 85·7; H, 6·6%).

Replacement of nitrobenzene by carbon disulphide (450 ml.) in the above experiment yielded mainly unchanged acenaphthene; when the reaction mixture was refluxed for 6 hr., however, 1-propionylacenaphthene, m. p. and mixed m. p. 119—120° (20 g., 16·3%), and the 3-isomer, m. p. and mixed m. p. 65—66° (67 g., 54·6%), were isolated, identical with the above products.

1-Propionylacenaphthene in dry ethanol gave a picrate, orange needles, m. p. 123—124°, and a 1 : 3 : 5-*trinitrobenzene* complex, pale yellow needles, m. p. 123—126° (Found: C, 60·0; H, 4·1; N, 10·1. $C_{21}H_{17}O_7N_3$ requires C, 59·6; H, 4·0; N, 9·9%); the 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid in orange needles, m. p. 254—256° (Found: C, 64·4; H, 4·7; N, 14·0. $C_{21}H_{18}O_4N_4$ requires C, 64·6; H, 4·6; N, 14·35%).

3-Propionylacenaphthene afforded a *trinitrobenzene derivative* (from ethanol), yellow needles, m. p. 99—100° (Found: C, 59·7; H, 4·0; N, 10·1%), and a 2 : 4-*dinitrophenylhydrazone* (from acetic acid), orange needles, m. p. 232—234° (Found: C, 64·7; H, 4·4; N, 14·2%).

2- *and* 4-*Propionylnaphthalic Anhydride.*—1-Propionylacenaphthene (4 g.) in boiling acetic acid (150 ml.) was treated with sodium dichromate (20 g.) during 30 min. After 2 hours' refluxing and addition to ice water, the resulting solid was collected and extracted with hot 5% aqueous sodium carbonate solution (250 ml.), and the alkaline extract acidified with hydrochloric acid; the precipitate was filtered off and crystallised from acetic acid in pale brown plates, m. p. 198° (4·3 g., 88·9%) (Found: C, 70·5; H, 4·2. $C_{15}H_{10}O_4$ requires C, 70·9; H, 3·9%), of 2-*propionylnaphthalic anhydride*. Refluxing with a large excess of aqueous ammonia (*d* 0·88) and a little ethanol for 45 min. afforded the *naphthalimide*, which crystallised from ethanol in silky needles, m. p. 254—255° (Found: C, 71·2; H, 4·25; N, 5·2. $C_{15}H_{11}O_3N$ requires C, 71·15; H, 4·35; N, 5·5%).

4-*Propionylnaphthalic anhydride*, pale yellow needles, m. p. 270° (from acetic acid) (4 g., 82·6%) (Found: C, 70·5; H, 3·7%), gave the corresponding *naphthalimide*, pale yellow needles (from ethanol), m. p. 230—231° (Found: C, 70·0; H, 4·15; N, 5·6%).

1- *and* 3-n-*Propylacenaphthene.*—1-Propionylacenaphthene (15 g.), toluene (150 ml.), hydrochloric acid (200 ml.), and water (50 ml.) were refluxed, and amalgamated zinc (from 75 g. of zinc and 5% aqueous mercuric chloride) was added; after 5 hours' stirring under reflux, hydrochloric acid (20 ml.) and water (5 ml.) were added and the mixture refluxed for a further 3 hr. Toluene was removed from the dried toluene layer, and the residue distilled, to give 1-n-*propylacenaphthene* as an almost colourless oil, b. p. 172—176°/6 mm. (5·6 g., 40%) (Found: C, 91·4; H, 8·0. $C_{15}H_{16}$ requires C, 91·8; H, 8·2%). The *picrate* crystallised from dry ethanol in red needles, m. p. 94—95° (Found: C, 59·35; H, 4·2; N, 9·5. $C_{21}H_{19}O_7N_3$ requires C, 59·3; H, 4·5; N, 9·9%), and the 1 : 3 : 5-*trinitrobenzene derivative* in fine yellow needles, m. p. 103—104°, from dry ethanol (Found: C, 61·7; H, 4·9; N, 10·5. $C_{21}H_{19}O_6N_3$ requires C, 61·6; H, 4·65; N, 10·3%).

3-Propionylacenaphthene similarly afforded 3-n-*propylacenaphthene*, b. p. 169—172°/4 mm. (5·2 g., 37%) (Found: C, 91·8; H, 7·9%); the derived *picrate* crystallised from dry ethanol in red needles, m. p. 79—80° (Found: C, 59·4; H, 4·5; N, 9·6%), and the *trinitrobenzene complex* (from dry ethanol) in orange needles, m. p. 81—82° (Found: C, 61·9; H, 4·7; N, 10·3%).

2- *and* 4-n-*Propylnaphthalic Anhydride.*—1-n-Propylacenaphthene (4 g.) was oxidised by sodium dichromate (25 g.) in boiling acetic acid (150 ml.) for 3 hr.; addition to ice-water gave a precipitate, which was extracted twice with hot 5% aqueous sodium carbonate (200 ml.), and the alkaline extract was acidified with hydrochloric acid. 2-n-*Propylnaphthalic anhydride*

crystallised from acetic acid in colourless plates, m. p. 161—162° (4·5 g., 91%) (Found: C, 74·6; H, 4·9. $C_{15}H_{12}O_3$ requires C, 75·0; H, 5·0%). The *naphthalimide* crystallised from ethanol in needles, m. p. 240—241° (Found: C, 75·6; H, 5·4; N, 6·0. $C_{15}H_{13}O_2N$ requires C, 75·3; H, 5·4; N, 5·9%).

4-n-*Propylnaphthalic anhydride*, prepared from 3-*n*-propylacenaphthene (4 g.) in similar manner, crystallised from acetic acid in pale yellow crystals, m. p. 123—124° (4·3 g., 87·7%) (Found: C, 74·7; H, 5·2%); the corresponding *naphthalimide* crystallised from ethanol in colourless needles, m. p. 211—211·5° (Found: C, 75·3; H, 5·25; N, 6·1%).

Oxidation of 4-n-*Propylnaphthalic Anhydride*.—Potassium permanganate (6 g.) in hot water (120 ml.) was added to a solution of 4-*n*-propylnaphthalic anhydride (1 g.) in boiling 5% aqueous sodium hydroxide (120 ml.), and the mixture heated at 95° for 2 hr.; after removal of excess of permanganate with alcohol and filtration, the filtrate was acidified with hydrochloric acid and extracted with chloroform; the residue from the chloroform crystallised from acetic acid in almost colourless needles, m. p. 273°, of 4-carboxynaphthalic anhydride (0·1 g.), not depressed in m. p. on admixture with the product obtained from 4-acetylnaphthalic anhydride (Nursten and Peters [4]). Resins only were obtained in a similar oxidation of 2-*n*-propylnaphthalic anhydride.

3 : 4-*Dipropionylacenaphthene*.—By the procedure described for monopropionylacenaphthenes acenaphthene (90 g.), anhydrous aluminium chloride (168 g.), propionyl chloride (108 g.), and carbon disulphide (900 ml.) afforded a black tar, which was repeatedly extracted with benzene (charcoal). The pale brown residues obtained (90 g., 58%) after removal of benzene were crystallised three times from ethanol (charcoal) to give almost colourless needles, m. p. 120—121°, of 3 : 4-*dipropionylacenaphthene* (admixture with monopropionylacenaphthene, m. p. 119—120°, gave m. p. 96—108°) (Found: C, 81·2; H, 6·7. $C_{18}H_{18}O_2$ requires C, 81·2; H, 6·8%). It did not form a solid picrate, but gave a 2 : 4-*dinitrophenylhydrazone*, dark red needles (from acetic acid), m. p. 204—206° (Found: C, 63·0; H, 4·9; N, 14·05. $C_{24}H_{22}O_5N_4$ requires C, 64·6; H, 4·9; N, 12·6. $C_{30}H_{26}O_8N_8$ requires C, 57·5; H, 4·2; N, 17·9%); it is possible that steric hindrance is a factor limiting condensation with the keto-groups in positions 3 and 4.

3 : 4-*Di*-n-*propylacenaphthene*.—The above dipropionylacenaphthene (15 g.) was reduced in toluene (150 ml.), hydrochloric acid (400 ml.), and water (100 ml.) by amalgamated zinc (from 150 g. of zinc); after 4 hours' refluxing, the usual procedure afforded a glass which distilled as an oil (b. p. 184—188°/4 mm.) and then solidified; crystallisation from ethanol gave very slowly pale yellow needles, m. p. 26—27° (Found: C, 90·6; H, 9·1. $C_{18}H_{22}$ requires C, 90·8; H, 9·2%), of 3 : 4-*di*-n-*propylacenaphthene*. The 1 : 3 : 5-*trinitrobenzene derivative* crystallised from dry ethanol in red needles, m. p. 74° (Found: C, 63·9; H, 5·5; N, 9·1. $C_{24}H_{25}O_6N_3$ requires C, 63·9; H, 5·5; N, 9·3%). A solid picrate could not be prepared, the product being a dark red oil.

Oxidation of 3 : 4-*Di*-n-*propylacenaphthene*.—Oxidation of 3 : 4-di-*n*-propylacenaphthene (4 g.) and sodium dichromate (25 g.) in boiling acetic acid (150 ml.) for 2 hr., followed by purification through aqueous sodium carbonate, gave pale brown needles, m. p. 126—127° (from acetic acid), of 4 : 5-*di*-n-*propylnaphthalic anhydride* (4 g., 64%) (Found: C, 76·3; H, 6·1. $C_{18}H_{18}O_3$ requires C, 76·6; H, 6·4%). The *naphthalimide* crystallised from ethanol in pale yellow leaflets, m. p. 118—120° (Found: C, 76·7; H, 6·5; N, 5·4. $C_{18}H_{19}O_2N$ requires C, 76·9; H, 6·8; N, 5·0%).

Further oxidation of 4 : 5-di-*n*-propylnaphthalic anhydride (1·5 g.) was effected by heating it with nitric acid (*d* 1·42; 8 ml.) and water (4 ml.) at 170—180° for 24 hr. A trace of colourless solid, m. p. 238°, was filtered off, and the filtrate evaporated carefully to yield a pale brown solid which separated from water as an almost colourless solid, m. p. 238°; after melting and resolidifying, the residue had m. p. 193—198° (benzene-1 : 2 : 3 : 4-tetracarboxylic acid has m. p. 138°, and its anhydride, m. p. 193—196°); ethereal diazomethane in dry ether gave, in 30 min., after removal of ether, a solid which crystallised from methanol in needles, m. p. 128—129°, identical with tetramethyl benzene-1 : 2 : 3 : 4-tetracarboxylate, m. p. and mixed m. p. 128—129°, obtained from 4-acetylnaphthalic anhydride by Nursten and Peters.[4]

CLOTHWORKERS' RESEARCH LABORATORY,
THE UNIVERSITY, LEEDS.

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707. *The Kinetics of Catalytic Polymerisations. Part XII.*[1] *Heat and Mechanism of Polymerisation of α-Methylstyrene catalysed by the Chloroacetic Acids.*[1]

By C. P. Brown and A. R. Mathieson.

The heat of polymerisation of α-methylstyrene catalysed by trichloroacetic acid in ethylene dichloride at 20° is 8280 ± 90 cal. mole^{-1}. The polymer formed is a mixture of unsaturated dimer and trimer, and saturated esterified dimer–pentamer. The heat of polymerisation and infrared spectra are in agreement with the presence of trichloroacetate-substituted phenylindane end-groups in the saturated esterfied fraction. The ceiling temperature for polymerisation is 60°. The established kinetics of polymerisation have been confirmed by an adiabatic method. The mechanism of polymerisation is similar to that for styrene with the addition of depropagation and a two-step termination. Formation of the monomer–catalyst complex before initiation can explain differences between kinetic orders obtained from the initial rates and during the course of reaction.

The methyl substituent in α-methylstyrene increases the rate of cationic polymerisation but confines it to the formation of very low polymer at ordinary temperatures.[1] Evans and Polanyi [2] and Flory [3] suggested that for 1 : 1-disubstituted ethylenes there is steric hindrance to polymerisation, and in general heats of polymerisation ($-\Delta H_p$) for disubstituted monomers are 3—9 kcal. mole^{-1} smaller than the values estimated from heats of formation and hydrogenation, allowance being made for increased branching in the polymers and end effects.[4] For dienes and phenyl-substituted vinyl monomers the loss of resonance stabilisation on polymerisation must be also taken into account. The discrepancy is considered to be due to the energy of steric repulsion between the side-groups on the polymer chain.[4,5] Estimated values of $-\Delta H_p$ of 22·3, 18·7, and 18·0 kcal. mole^{-1} have been given for ethylene, styrene, and α-methylstyrene respectively,[4] and values of 16·1—17·54 have been obtained experimentally for styrene.[6,7] This indicates only a small degree of steric repulsion corresponding to about 1 kcal. mole^{-1}, loss of resonance stabilisation accounting for about 4 kcal. mole^{-1}.

Roberts and Jessup [8] measured the heat of polymerisation for four fractions of poly-α-methylstyrene formed during the industrial distillation of α-methylstyrene. The heat of polymerisation decreased as molecular weight ($\overline{M}_n$) increased from 10·13 kcal. ($\overline{M}_n = 1300$) to 8·83 kcal. mole^{-1} ($\overline{M}_n = 5400$), and obeyed the relation

$$-\Delta H_p = 8{\cdot}424 + 2194/\overline{M}_n$$

Extrapolation, if valid, shows that the infinite polymer has $-\Delta H_p = 8{\cdot}4$ kcal. mole^{-1} and the values for the dimer, trimer, and tetramer are 17·7, 14·6, and 13·0 kcal. mole^{-1} respectively. These figures apply to saturated polymers containing no catalyst fragments. The value for the infinite polymer indicates a very large steric effect accounting for about 9 kcal. mole^{-1}, while the dimer shows little, if any, steric hindrance. McCormick [9] gives $-\Delta H_p = 6{\cdot}96$ kcal. mole^{-1} for the polymerisation with a sodium–naphthalene catalyst, calculated from measurements of the ceiling temperature. In view of the partial

[1] Part XI, Brown and Mathieson, *J.*, 1958, 3445.
[2] Evans and Polanyi, *Nature*, 1943, **152**, 738.
[3] Flory, *J. Amer. Chem. Soc.*, 1943, **65**, 372.
[4] Flory, "Principles of Polymer Chemistry," Cornell Univ. Press, Ithaca, New York, 1953, pp. 249—256.
[5] Roberts, *J. Res. Nat. Bur. Stand.*, 1950, **44**, 221.
[6] Tong and Kenyon, *J. Amer. Chem. Soc.*, 1947, **69**, 1402.
[7] Roberts, Watson, and Jessup, *J. Res. Nat. Bur. Stand.*, 1947, **38**, 627.
[8] Roberts and Jessup, *ibid.*, 1951, **46**, 11.
[9] McCormick, *J. Polymer Sci.*, 1957, **25**, 488.

incorporation of catalyst for chloroacetic acid catalysis,[1] measurement of $-\Delta H_p$ for this system might give information on the structure of the polymer, and perhaps on its mechanism of formation. The opportunity was taken to confirm the kinetic orders of the polymerisations with the adiabatic calorimeter.

Results and Discussion

Heat of Polymerisation.—The heat of polymerisation of α-methylstyrene catalysed by trichloroacetic acid in ethylene dichloride solution was measured calorimetrically at 20° (Table 1); the results were averaged to give 8280 ± 90 cal. mole^{-1} for $-\Delta H_p$, the accuracy being estimated from the reproducibility since the calorimetric measurements were more accurate than the polymerisations were reproducible.

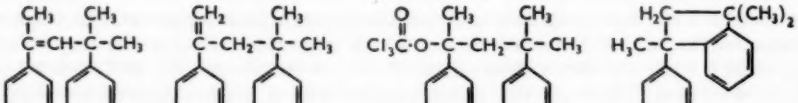
The molecular weight and distribution of the polymer formed were $\overline{M}_n = 370$; fraction 236—350, 58·9%; fraction 350—500, 25·3%; fraction 500—800, 13·9%; the constitution was unsaturated dimer, 47%; unsaturated trimer, 12%; dimer ester, 25%; trimer—pentamer ester, 14% (w/w).[1]

The value of $-\Delta H_p$ is close to that for an infinite polymer,[8] but for a comparable polymer of $\overline{M}_n = 370$, Roberts and Jessup's results predict $-\Delta H_p = 14{\cdot}35$ kcal. mole^{-1}, greatly in excess of the value obtained here. The polymer studied by Roberts and Jessup was saturated and incorporated no catalyst fragments. The double bonds and trichloroacetate groups in our polymer will have a large influence on $-\Delta H_p$.

Table 1. *Heat of polymerisation of α-methylstyrene.*

Monomer polymerised (mole)	0·0737	0·1370	0·0608	0·1410	0·1350
Corrected reaction temp. rise (°)...	2·009	3·452	1·772	3·471	3·524
Corrected rating temp. rise (°).....	0·902	0·432	0·945	0·543	0·543
Electrical energy supplied (cal.) ...	272·41	142·24	271·65	182·98	170·68
Thermal equivalent (cal.)	302·00	329·26	287·46	336·97	314·33
Heat evolved (cal.)	606·72	1136·61	509·38	1168·99	1107·69
Heat of polymerisation (cal.)	8232·2	8292·7	8377·2	8290·8	8205·1

Structure of the Polymer.—Head-to-tail addition being assumed, the simplest structures for the unsaturated dimer are (I) and (II). Corresponding structures could be written for head-to-head and tail-to-tail addition. The polymer could be a mixture of (I) and (II), as already reported,[10] which might behave as a single structure in heterolytic reactions. If there is no steric strain in this dimer, as implied by Roberts and Jessup's results,[8] its heat of formation from monomer will be equal to the heat of formation of a hypothetical unstrained infinite polymer from this dimer, the heats of formation being reckoned per monomer unit. The heat of formation of saturated dimer from monomer (17·7 kcal. mole^{-1}) being taken as equal to the heat of formation of hypothetical unstrained infinite



polymer from monomer, the heat of dimerisation to unsaturated dimer is 8·85 kcal. mole^{-1}. The heat of trimerisation [8] to saturated trimer is 14·6 kcal. mole^{-1} and so the heat of trimerisation to unsaturated trimer is 9·7 kcal. mole^{-1}. The contribution of the unsaturated fraction 236—350 (59%) to the total heat of polymerisation is therefore 5·3 kcal. mole^{-1}.

[10] Hukki, *Acta Chem. Scand.*, 1949, **3**, 279.

The formation of the C–O bond will have an important influence on the heat of polymerisation to the esterified polymers. Values of 79, 80, 98·2, and 145 kcal. mole^{-1} may be taken for the C–O, C–C, C–H, and C=C bond energies respectively,[11] and rupture of the O–H bond in trichloroacetic acid yields [12] 3·2 kcal. mole^{-1}. The heat of dimerisation to a simple straight-chain esterified dimer (III) is largely the heat change associated with the conversion of 2 C=C and 1 O–H bonds into 3 C–C, 1 C–H, and 1 C–O bond, and if 4 kcal. mole^{-1} are allowed for loss of resonance stabilisation, it is 58 kcal. mole^{-1} which is much too high to reconcile with the experimental result even though the calculation is approximate. The corresponding value for linear esterified trimer is 41 kcal. mole^{-1}, 3 kcal. being allowed for steric strain. Polymers having this type of structure (III) cannot be formed in this reaction.

The stannic chloride-catalysed polymerisation of α-methylstyrene has been reported to yield cyclised polymers having a terminal substituted phenylindane structure,[13] and this structure (IV) has been assigned to the saturated dimer.[14] Infrared analysis of poly-α-methylstyrene formed by trichloroacetic acid catalysis [1] indicated the presence of trichloroacetic groups and the possibility of the occurrence of CH groups and *ortho*-disubstitution. A feasible structure of the saturated esterfied dimer is therefore (IV) with the trichloroacetate group substituted on the methylene group. Its formation from monomer and acid involves conversion of 2 C=C, 1 C–H, and 1 O–H bond into 4 C–C and 1 C–O bond, and so the heat of dimerisation is ~4·0 kcal. mole^{-1}. Heats of polymerisation to the corresponding trimer, tetramer, and pentamer are 7·6, 8·9, and 9·7 kcal. mole^{-1} respectively. The contribution of the esterified fraction 350—800 (39%), if it has this type of structure, to the total heat of polymerisation is ~2·3 kcal. mole^{-1}, the trimer–pentamer mixtures being treated as a tetramer. Together with the calculated contribution from the unsaturated fraction, this gives a calculated heat of polymerisation of 7·6 kcal. mole^{-1}, which is comparable with the experimental value when the approximate nature of the calculation is considered. This provides further support for the occurrence of the terminal substituted phenylindane structure in the saturated polymers.

Ceiling Temperature for Polymerisation.—The variation of the degree of polymerisation (n) with temperature and monomer concentration ([M]) can be derived from the kinetic definition of n in terms of chain propagation and termination as

$$\ln 1/n = E_n/RT + \ln 1/[\mathrm{M}] + \text{Const.}$$

where E_n is the "activation energy for degree of polymerisation," normally given by $E_n = \sum E_p - \sum E_t$ where $\sum E_p$ and $\sum E_t$ are the activation energies for all types of propagation and chain-breaking process respectively. McCormick [9] has demonstrated the linearity of ln ($1/n$) with ln ($1/[\mathrm{M}]$) for α-methylstyrene, and the linearity of ln ($1/n$) with ln ($1/T$) is illustrated in Fig. 1 for the trichloroacetic acid-catalysed polymerisations of styrene and α-methylstyrene. The ceiling temperature (T_c) is obtained when ln ($1/n$) = 0 and is 60° for α-methylstyrene, in agreement with values obtained for this monomer in other systems.[9,15]

Entropy of Polymerisation.—Dainton and Ivin's equation [15] $T_c = \Delta H_p/(\Delta S° + R \ln [\mathrm{M}])$ ($\Delta S°$ is the standard entropy of polymerisation) gives $\Delta S° = -24·8$ cal. deg.$^{-1}$ mole^{-1} for the trichloroacetic acid-catalysed polymerisation of α-methylstyrene, the same value as given by McCormick for the sodium–naphthalene catalysis.[9]

Depropagation.—Depropagation is important [16] for some free-radical [17] and anionic [18]

[11] Pitzer, *J. Amer. Chem. Soc.*, 1948, **70**, 2140.
[12] Bichowsky and Rossini, "The Thermochemistry of the Chemical Substances," Reinhold Publ. Corp., New York, 1936.
[13] Dainton and Tomlinson, *J.*, 1953, 151.
[14] Bergmann, Taubadel, and Weiss, *Ber.*, 1931, **64**, 1493.
[15] Dainton and Ivin, *Trans. Faraday Soc.*, 1950, **46**, 331.
[16] *Idem*, *Nature*, 1948, **162**, 705.
[17] *Idem*, *Proc. Roy. Soc.*, 1952, *A*, **212**, 207.
[18] Swarc, Levy, and Milkovich, *J. Amer. Chem. Soc.*, 1956, **78**, 2656.

polymerisations near the ceiling temperature. Even at −40° the anionic polymerisation of α-methylstyrene shows propagation–depropagation equilibrium,[19] but the cationic polymerisation catalysed by the boron trifluoride ether complex has too low an equilibrium concentration of monomer at −20° for depropagation to be important, and it has been concluded that the low degree of polymerisation is due to a slow propagation with a normal rapid termination.[20]

The propagation step in the chloroacetic acid-catalysed polymerisation of styrene can be written [21]

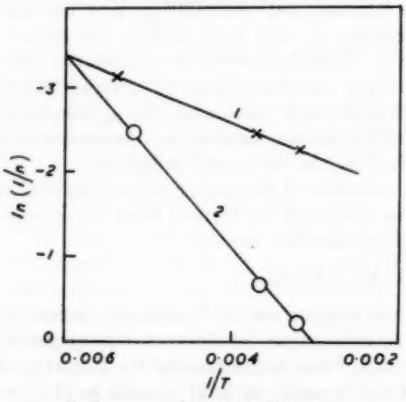
$$(M_n^+C^-)C + M \longrightarrow (M_{n+1}^+C^-)C$$

and the similarity of the kinetics suggests that this applies to α-methylstyrene also. The importance of depropagation for α-methylstyrene is determined by treating this as an equilibrium for which the equilibrium constant at 25° is, from $-\Delta H_p$ and $\Delta S°$,

$$K_{pd} = k_p/k_d = [(M_{n+1}^+C^-)C]/\{[(M_n^+C^-)C][M]\} = 4{\cdot}47$$

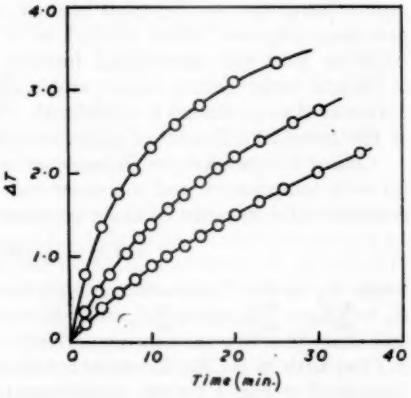
and the equilibrium monomer concentration ($[M]_e$) for $[(M_{n+1}^+C^-)C] = [(M_n^+C^-)C]$ is 0·224M. The depropagation will be significant for this system. Since the molecular-weight distribution does not change appreciably during polymerisation,[1]

FIG. 1. *Effect of temperature on degree of polymerisation (n).*



1, Styrene; 2, α-methylstyrene.

FIG. 2. *Adiabatic polymerisation catalysed by trichloroacetic acid in ethylene dichloride solution.*



$[(M_3^+C^-)C]/[(M_2^+C^-)C]$ is likely to be equal to the ratio of trimer to dimer in the polymer. Assuming that the trimer–pentamer ester mixture is half trimer, we find

$$[(M_3^+C^-)C]/[(M_2^+C^-)C] = 0{\cdot}29 \text{ and } [M]_e = 0{\cdot}065\text{M}$$

for dimer–trimer propagation–depropagation equilibrium. So although depropagation is important in fixing the ceiling temperature some other process, termination or transfer, is largely responsible for breaking the chains and producing very low polymer.

Kinetics by Adiabatic Calorimetry.—The adiabatic calorimeter was used to follow the temperature rise during polymerisation to confirm the kinetic orders established for both styrene and α-methylstyrene. Fig. 2 shows some typical time–temperature curves for α-methylstyrene catalysed by trichloroacetic acid in ethylene dichloride. The initial

[19] Worsfold and Bywater, *J. Polymer Sci.*, 1957, **26**, 299.
[20] *Idem*, *J. Amer. Chem. Soc.*, 1957, **79**, 4917.
[21] Brown and Mathieson, *J.*, 1957, 3631.

rates of the reactions studied are shown in Table 2 with the appropriate concentration functions. This method fully confirms the kinetic orders of the initial rates already established, *i.e.*,

$$-d[M]_0/dt = k_0[M]_0^2[C]_0 \text{ (nitromethane solutions)}$$

$$-d[M]_0/dt = k_0[M]_0^2[C]_0^2 \text{ (ethylene dichloride solutions)}$$

$$-d[M]_0/dt = k_0[M]_0^2[C]_0^x,\ x = 3{\cdot}51 \text{ (styrene)};\ \ x = 3{\cdot}2 \text{ (α-methylstyrene)}$$

TABLE 2. *Dependence of initial rates on concentration by the adiabatic method. Trichloroacetic acid catalysis at 20°.*

α-Methylstyrene (no solvent)		α-Methylstyrene in ethylene dichloride		Styrene in nitromethane	
Initial rate (deg. min.$^{-1}$)	$10^2[M]_0^2[C]_0^2$	Initial rate (deg. min.$^{-1}$)	$[M]_0^2[C]_0^2$	Initial rate (deg. min.$^{-1}$)	$[M]_0^2[C]_0$
0·100	1·0	0·019	0·65	0·012	0·95
0·104	1·5	0·042	1·02	0·015	1·20
0·108	2·4	0·048	1·35	0·022	1·65
0·115	5·7	0·056	1·90	0·029	2·30
0·131	10	0·092	2·55	—	—
0·141	14	—	—	—	—

Mechanism of the Polymerisations

The results presented here and in the preceding Part[1] indicate that the chloroacetic acid-catalysed polymerisations of α-methylstyrene proceed essentially by the mechanisms established for styrene,[21] with the addition of depropagation, except that the termination occurs by proton expulsion to form unsaturated polymer, some of which reacts with catalyst to form chloroacetate-substituted phenylindane end groups. The relative rates of propagation, termination, and transfer are different for the two monomers. The mechanisms for α-methylstyrene are summarised in Table 3.

TABLE 3. *Mechanism of polymerisation.*

	No solvent	Ethylene dichloride solution	Nitromethane solution
1.	$M + C \underset{k_1'}{\overset{k_1}{\rightleftharpoons}} MC$ . . . . . (K_1)		
1*a*.	$M + C_2 \rightleftharpoons MC_2$ . . . . . (K_2)		
2.	$M + CW \xrightarrow{k_i} M^+C^- + W$	$MC \xrightarrow{k_i} M^+C^-$	
2*a*.	$MC_2 + CW \xrightarrow{k_i'} M^+C^- + C_2 + W$		
3.	$M^+C^- + MC \underset{k_{d_1}}{\overset{k_p}{\rightleftharpoons}} (M_2^+C^-)C$		$M^+C^- + M \underset{k_d}{\overset{k_p}{\rightleftharpoons}} M_2^+C^-$
3*a*.	$(M_n^+C^-)C + M \underset{k_d}{\overset{k_p}{\rightleftharpoons}} (M_{n+1}^+C^-)C$		$M_n^+C^- + M \rightleftharpoons M_{n+1}^+C^-$
4.	$(M_n^+C^-)C + M \xrightarrow{k_{tr}} M_n + (M^+C^-)C$		$M_n^+C^- + M \xrightarrow{k_{tr}} M_n + M^+C^-$
5.	$(M_n^+C^-)C \xrightarrow{k_h} M_n + C_2$		$M_n^+C^- \xrightarrow{k_h} M_n + C$
6.	$M_n + C \underset{k_c'}{\overset{k_c}{\rightleftharpoons}} M_nC$ . . . . . (K_c)		

Step 1 is the reversible formation of the monomer–catalyst complex MC, and a second complex MC_2 is formed in absence of solvent (step 1*a*). Initiation (step 2) is the spontaneous conversion of the complex MC into an ion-pair, which in absence of solvent requires cocatalysis by water (W) and may involve MC_2 also (step 2*a*). Propagation–depropagation

(step 3*a*) is written differently for the first stage (step 3) to allow for solvation of the ion-pair by catalyst in ethylene dichloride and absence of solvent. The ion-pair is not catalyst-solvated in nitromethane. Steps 4 and 5 are transfer and spontaneous termination and step 6 is the reversible formation of esterified from unsaturated polymer. There is no evidence for non-stationary conditions and the stationary-state assumption is not necessarily invalidated by the low degree of polymerisation when transfer and depropagation reactions are important. However, k_p, k_d, k_{tr}, k_t, and k_c will not be independent of chain-length and in the equations which follow these quantities will represent weighted means of the values for the different chain lengths.

If stationary conditions hold, the stationary concentration of ion-pairs ([G]) is

$$[G] = k_i[MC]/k_t \text{ (solution)}$$

$$[G] = (k_i[M][CW] + k_i^1[MC_2][CW])/k_t \text{ (absence of solvent)}$$

The initial rates of polymerisation are

$$-d[M]_0/dt = k_i[MC](k_p[M]_0[C]_0 - k_d)/k_t \text{ (ethylene dichloride solution)}$$

$$-d[M]_0/dt = k_i[MC](k_p[M]_0 - k_d)/k_t \text{ (nitromethane solution)}$$

$$-d[M]_0/dt = (k_i[M]_0[CW] + k_i^1[MC_2][CW])(k_p[M]_0[C]_0 - k_d)/k_t \text{ (absence of solvent).}$$

Since $k_p = 4{\cdot}47k_d$ and $[M]_0[C]_0 \gg 1$, k_d may be neglected for the initial rate. The observed change in kinetic order with respect to monomer as reaction proceeds [1] suggests a treatment of the formation of the MC complex similar to that for enzyme catalysis.[22] For a stationary concentration [MC]

$$d[MC]/dt = k_1[M]([C] - [MC]) - k_1^1[MC] - k_i[MC] = 0$$

$$[MC] = k_1[M][C]/(k_1[M] + k_1^1 + k_i)$$

and the rate of initiation (V_i) is

$$V_i = k_i[MC] = k_ik_1[M][C]/(k_1[M] + k_1^1 + k_i)$$

When $[C] \gg [MC]$, $V_i = k_ik_1[M][C]/(k_1^1 + k_i)$, and this holds for the initial rate. Hence, in agreement with the experimental kinetic orders

$$-d[M]_0/dt = k_ik_1k_p[M]_0^2[C]_0^2/k_t(k_1^1 + k_i) \text{ (ethylene dichloride solution)}$$

$$-d[M]_0/dt = k_ik_1k_p[M]_0^2[C]_0/k_t(k_1^1 + k_i) \text{ (nitromethane solution)}$$

$$-d[M]_0/dt = k_pK_h[M]_0^2[C]_0[W](k_i + k_i^1[C]_0^3K_2)/k_t \text{ (no solvent)}$$

$$\text{where } K_h = [CW]/[C][W]$$

After the initial stage is over the limiting rate of initiation is $V_i = k_i[C]_0$ if $k_1 \gg (k_1^1 + k_i)$ and so the rate of polymerisation becomes

$$-d[M]/dt = k_ik_p[M][C]^2/k_t \text{ (ethylene dichloride solution)}$$

$$-d[M]/dt = k[M][C][W](k_i + k_i^1[C]^3K_2) \text{ (no solvent)}$$

where k is written for the rate-constant product and steps 2 and 2*a* are considered to proceed analogously to the formation and ionisation of MC. The rate of polymerisation depends on [M] and not $[M]^2$ after the initial stage is over, as observed.[1] For nitromethane solutions, the ionisation of the monomer–catalyst complex is favoured by the high dielectric constant of the medium; [MC] is always very small and never becomes equal

[22] Michaelis and Menten, *Biochem. Z.*, 1913, **49**, 333.

to $[C]_0$ and the initial kinetics persist throughout the reaction, as observed. This treatment of the initiation applies to styrene as well as to α-methylstyrene.

The initial rate of catalyst consumption ($-d[C]_0/dt$) is determined by the first stage of propagation (step 3) for ethylene dichloride solutions and so shows the same kinetic order ($[M]_0^2[C]_0^2$) and has roughly the same magnitude as the initial rate of polymerisation, as observed.[1] In this solvent then,

$$[M^+C^-] = (k_i + k_{tr}[G])/(k_{tr} + k_{p1})$$

$$-d[C]_0/dt = k_i k_{p1} k_1([M]_0[C]_0 + k_{tr} k_1[M]_0^2[C]_0^2/k_t(k_1^1 + k_i)]/(k_{tr} + k_{p1})(k_1^1 + k_i)$$

$[M]_0[C]_0$ is evidently negligible compared with the term in $[M]_0^2[C]_0^2$ and this agrees with the preponderance of transfer over termination required by the molecular weights (see below) and the small value of $(k_1^1 + k_i)/k_1$ (the " Michaelis constant ") needed to explain the change in kinetic order with respect to monomer. The fall in catalyst consumption and the eventual catalyst regeneration are due to the release of catalyst by termination and transfer, only a part of the released catalyst combining with the polymer. For the reactions in the absence of solvent, initiation depends on [CW] which is small and proportional to [C] when [W] is constant. Hence $-d[C]_0/dt \propto [C]_0$ as observed.

The degree of polymerisation (n) is $n = (V_p - V_d)/(V_t + V_{tr})$ and is independent of [M] and [C] for ethylene dichloride solutions and absence of solvent. Then, since $V_d \ll V_p$, $V_{tr} \gg V_t$, and transfer is the most important polymer-chain-breaking process, and $k_p/k_{tr} = 2{\cdot}7$ at 25° (the corresponding value for styrene[21] is 21). The relatively high negative value of E_n will be due to a large E_{tr}, with a small E_t as for styrene.[23] The increase in n with [C] for nitromethane solutions requires a reduced transfer rate at high [C], or re-activation by the catalyst of terminated unsaturated polymer in preference to cyclisation.

The discussions of the initiation mechanism in terms of the formation of endothermic polarisation complexes with a finite probability of transition to ion-pairs, and of propagation in terms of autocatalysis given for styrene [21] apply equally to α-methylstyrene.

Experimental

Materials were purified as already described.[1] The calorimeter used for the measurement of heat of polymerisation and adiabatic kinetics was that previously employed for the measurement of heats of mixing of hydrocarbons.[24] For the heat of polymerisation experiments, known weights of acid and ethylene dichloride were distilled into glass ampoules which were sealed, and placed in the mixing vessel surrounded by a known mixture of ethylene dichloride and monomer. The procedure was as before [24] except that water at 20° replaced alcohol in the middle Dewar vessel, to increase the thermal equivalent. The temperature rises were kept below 4°. Polymerisation was complete, and the temperature constant, in less than 1 hr. Calibrations were carried out before and after polymerisation to determine the thermal equivalent of the system. Cooling corrections were negligible but the temperature was measured every minute for 15 min. before and after each polymerisation and calibration. The calibration results in Table 1 are the averages of the two determinations. The change in thermal equivalent on polymerisation was negligible. Comparison of experiments at different monomer concentrations indicated that the heat of dilution is negligible compared with that of polymerisation. The calorimetric apparatus was far more precise than necessary, having been designed for the measurement of very small heat changes. The adiabatic kinetic experiments were carried out in the same way except that the reactions were slower and the temperature was measured every 2 min. during the reaction.

Nottingham University. [*Received, May 19th*, 1958.]

[23] Brown and Mathieson, *J.*, 1957, 3612.
[24] Brown, Mathieson, and Thynne, *J.*, 1955, 4141.

708. *Antituberculosis Agents. Part III.* Pyridine-4-sulphonamides and -sulphonhydrazides.*

By A. M. Comrie and J. B. Stenlake.

Pyridine-4-sulphonamide and -sulphonhydrazide, and numerous derivatives of these, have been prepared. Pyridine-4-sulphonamide has little antibacterial activity, and none of the derivatives of pyridine-4-sulphonhydrazide has significant activity against *Myco. tuberculosis*.

Pyridine-4-sulphonhydrazide, the analogue of *iso*nicotinic acid hydrazide (isoniazid), and pyridine-4-sulphonamide were required for examination of their antituberculosis activity. King and Ware [1] failed to obtain the latter, being unable to prepare the sulphonyl chloride. They reported that sodium pyridine-4-sulphonate with phosphorus pentachloride gave 1 : 4-dihydro-4-imino-1-4'-pyridylpyridine or 1-4'-pyridyl-4-pyridone, together with phosphorus oxychloride and thionyl chloride. 4-Pyridthione with bromine in acetic acid [2] gave di-4-pyridyl disulphide, and with chlorine gave 4-chloropyridine and di-4-pyridyl sulphide. Intermediate formation of unstable pyridine-4-sulphonyl halide would account for all these products. We therefore tried, by modified procedures, to isolate the sulphonyl chloride. Since the end of our work, we found that Talik and Plazek [2] had prepared pyridine-4-sulphonamide, the related dimethylamide and 1-*iso*propylidene-2-pyridine-4'-sulphonylhydrazine by methods essentially similar to ours.

Chlorination of 4-pyridthione in glacial acetic acid (cf. Lee and Dougherty [3]) and treatment of the solution with ammonia gave di-4-pyridyl sulphide as described by King and Ware.[1] Attempts to precipitate the acid chloride hydrochloride were unsuccessful. The relatively high freezing point of glacial acetic acid would not permit reaction below 15°, but limited chlorination (10 min.) at 0° in concentrated hydrochloric acid [4] and treatment with ammonia gave di-4-pyridyl disulphide. More prolonged chlorination (2 hr.) under the same conditions, and evaporation at room temperature *in vacuo*, however, gave pyridine-4-sulphonic acid,[5] confirming the intermediate formation of the sulphonyl chloride. Pyridine-4-sulphonamide was however obtained by prolonged chlorination of 4-thiopyridone in concentrated hydrochloric acid at 0° and pouring of the product solution into aqueous ammonia. The identity of the product was confirmed by preparaton of a picrate and *N*-oxide (Naito *et al.*[4]). Contrary to the observations of Talik and Plazek [2] we find that the chlorination of 4-pyridthione to pyridine-4-sulphonyl chloride does not require the presence of 30% hydrogen peroxide.

An attempt to extend the above method to pyridine-4-sulphonhydrazide gave 4-pyridylhydrazine hydrochloride, probably arising from the sulphonhydrazide (unstable—see below), under the alkaline reaction conditions which obtain in the presence of excess of hydrazine. Nitrobenzene-*o*- and -*p*-sulphonamide and pyridine-2- and -4-sulphonamide 1-oxide [4] undergo comparable rearrangements with loss of sulphur dioxide in alkaline solution.

To avoid separation of a water-soluble and labile product from large amounts of hydrazine hydrochloride, we attempted isolation of the intermediate pyridine-4-sulphonyl chloride. Freeze-drying the chlorinated solution at −30° proved difficult owing to the high concentration of hydrochloric acid present. Reaction of the concentrate with hydrazine hydrate gave 4-pyridylhydrazine hydrochloride, 4-pyridylhydrazinium pyridine-4-sulphonate, and small quantities of two other products, which were not identified. More

* Part II, *J.*, 1956, 3892.

[1] King and Ware, *J.*, 1939, 873.
[2] Talik and Plazek, *Acta Polon. Pharm.*, 1955, **12**, 5, 179; *Chem. Abs.*, 1957, **51**, 17,911.
[3] Lee and Dougherty, *J. Org. Chem.*, 1940, **5**, 81.
[4] Caldwell and Kornfeld, *J. Amer. Chem. Soc.*, 1942, **64**, 1695; Naito and Dohmori, *Pharm. Bull.* (*Japan*), 1955, **3**, 38.
[5] Comrie and Stenlake, *J.*, 1958, 1853.

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rapid concentration of the chlorinated solution at 0°, and treatment with hydrazine hydrate, yielded hydrazine sulphate as the only identifiable product. Pyridine-4-sulphonyl chloride was finally isolated as an oil from the chlorination of 4-thiopyridone in concentrated hydrochloric acid at 0° by neutralisation with calcium carbonate and rapid extraction into chloroform. Reaction of this solution with anhydrous hydrazine gave pyridine-4-sulphonhydrazide, whose identity was confirmed by its ability to reduce cold ammoniacal silver nitrate solution, and by the preparation of a picrate and other derivatives. Pyridine-4-sulphonhydrazide slowly decomposes in the solid state at room temperature, and more rapidly in solution in water, methanol, or ethanol even at 0°.

Alkyl,[7] alkylidene,[8] and aralkylidene [9] derivatives of *iso*nicotinoylhydrazine, not only retain the same level of antituberculosis activity, but also are less toxic than the parent compound. The 1-alkylidene- and 1-aralkylidene-2-pyridine-4′-sulphonylhydrazines listed in Table 1 have been prepared and, except for the ethylidene derivative, are stable in

TABLE 1. *1-Alkylidene and 1-aralkylidene-2-pyridine-4′-sulphonylhydrazines.*

1-Substituent	M. p. (decomp.)	Yield (%)	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H
Ethylidene	120°	42	$C_7H_9O_2N_3S$	42·5	4·1	42·2	4·55
*iso*Propylidene	147	59	$C_9H_{11}O_2N_3S$	45·5	5·2	45·1	5·2
1-Phenylethylidene	148—149	76	$C_{13}H_{13}O_2N_3S$	57·0	4·7	56·7	4·8
2-Phenylethylidene	118	80	$C_{13}H_{13}O_2N_3S$	56·9	4·5	56·7	4·8
*cyclo*Hexylidene	142	75	$C_{13}H_{15}O_2N_3S$	52·4	5·7	52·2	6·0
*cyclo*Heptylidene	166	86	$C_{14}H_{17}O_2N_3S$	54·0	6·2	53·9	6·4
Benzylidene	141—142	88	$C_{13}H_{11}O_2N_3S$	55·3	4·2	55·2	4·3
p-Hydroxybenzylidene	168—169	71	$C_{13}H_{11}O_3N_3S$	51·9	4·0	52·0	4·0
p-Methoxybenzylidene	155—156	86	$C_{14}H_{13}O_3N_3S$	54·0	4·2	53·6	4·5
Salicylidene	166	89	$C_{13}H_{11}O_3N_3S$	52·1	4·3	52·0	4·0
Vanillylidene	120—121	65	$C_{14}H_{13}O_4N_3S$	51·3	4·7	50·8	4·3
Piperonylidene	163—164	83	$C_{13}H_{11}O_4N_3S$	51·5	3·8	51·2	3·6
p-Dimethylaminobenzylidene	180	76	$C_{14}H_{16}O_2N_4S$	55·4	5·4	55·3	5·3
m-Methylbenzylidene	136—137	77	$C_{14}H_{13}O_2N_3S$	56·9	4·8	56·7	4·8
Cinnamylidene	148	89	$C_{14}H_{13}O_2N_3S$	58·8	4·5	58·5	4·6
Veratrylidene	164—165	65	$C_{14}H_{15}O_4N_3S$	52·1	4·2	52·3	4·7
Hexahydro-2 : 4 : 6-trioxo-5-pyrimidylidene	>360	99	$C_9H_7O_5N_5S,H_2O$	34·5	3·2	34·3	2·9
D-Glucosyl *	156	50	$C_{11}H_{17}O_7N_3S$	39·4	5·0	39·4	5·1
$CH_3(CMe{:}N{\cdot}NHX)_2$ †	162—163	92	$C_{15}H_{16}O_4N_6S_2$	N = 20·5		N = 20·5	

* Structure of sugar residue uncertain, but probably cyclic. † Product from acetylacetone.

TABLE 2. *1-Acyl-2-pyridine-4′-sulphonylhydrazines.*

Acyl	M. p. (decomp.)	Yield (%)	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H
Acetyl	181—182°	65	$C_7H_9O_3N_3S$	39·2	3·7	39·1	4·2
Benzoyl	164 *	40	$C_{13}H_{11}O_3N_3S$	51·9	4·0	52·0	4·0
β-Hydroxycarbonylpropionyl	179—180	73	$C_9H_{11}O_5N_3S$	39·4	4·3	39·6	4·1
o-Hydroxycarbonylbenzoyl	158	60	$C_{13}H_{11}O_5N_3S$	49·0	3·3	48·6	3·45
β-Hydroxycarbonylacryloyl	166—167	86	$C_9H_9O_5N_3S$	40·1	3·3	39·9	3·35
*iso*Nicotinoyl	120—121	20	$C_{12}H_{14}O_4N_4S$ †	46·3	4·5	46·45	4·55
Benzenesulphonyl	142—143	40	$C_{11}H_{11}O_4N_3S_2$	42·3	3·7	42·2	3·5
p-Toluenesulphonyl	153—154	40	$C_{12}H_{13}O_4N_3S_2$	44·0	4·0	44·0	4·0
Pyridine-4′-sulphonyl	173—174	60	$C_{10}H_{10}O_4N_4S_2$	38·5	3·6	38·2	3·2

* After drying *in vacuo*. The hemihydrate (from water) has m. p. 128—129°. † Found: N, 17·7. Reqd.: N, 18·1%.

the solid state and in solution. Contrary to Talik and Plazek,[2] we find that the 2-*iso*propylidene compound readily forms a picrate. Attempts to prepare the 4-pyridylmethylene and the furfurylidene derivative were unsuccessful, but the latter was obtained as its picrate.

[6] Naito, Dohmori, and Shimoda, *Pharm. Bull.* (*Japan*), 1955, **3**, 34.
[7] Fox and Gibas, *J. Org. Chem.*, 1953, **18**, 994; Fox, *ibid.*, p. 990.
[8] Fox and Gibas, *ibid.*, p. 983.
[9] Bavin, Drain, Seiler, and Seymour, *J. Pharm. Pharmacol.*, 1952, **4**, 844.

The 1-acyl-2-pyridine-4′-sulphonylhydrazines listed in Table 2 have also been prepared (cf. Fox and Gibas [10]) from the sulphonhydrazide and acid anhydride. 1-Phenylcarbamoyl- and 1-allylthiocarbamoyl-2-pyridine-4′-sulphonylhydrazine were obtained by condensation with phenyl *iso*cyanate and allyl *iso*thiocyanate respectively. The sulphonhydrazide with ethyl acetoacetate gave 3-methyl-1-pyridine-4′-sulphonyl-5-pyrazolone, and with acetylacetone gave 2 : 4-di(pyridine-4′-sulphonamidoimino)pentane rather than the expected pyrazole.

Condensation of pyridine-4-sulphonhydrazide with benzene-, toluene-*p*-, and pyridine-4-sulphonyl chloride yielded 1 : 2-disulphonylhydrazines. 1 : 2-Di(pyridine-4′-sulphonyl)-hydrazine could not, however, be obtained directly from hydrazine and excess of pyridine-4-sulphonyl chloride (see Dann and Davies [11]).

Attempts to reduce the *iso*propylidene and benzylidene derivative to the *iso*propyl and benzyl derivative catalytically and with sodium borohydride were unsuccessful. Condensation of the sodio-derivative of pyridine-4-sulphonhydrazide with benzyl chloride also failed to yield the required compound, giving instead benzyl 4-pyridyl sulphone.[12]

Although possibly an alternative route to pyridine-4-sulphonhydrazide, reaction of the sulphonamide with an excess of hydrazine for a limited time gave a crystalline product, tentatively identified as ammonium 4-pyridylhydrazinium thiosulphate, and equimolar proportions in dry methanol gave after 6½ hr. also 4-pyridylhydrazinium pyridine-4-sulphonate.

We thank Dr. E. O. Morris of this College for the bacteriological examination of pyridine-4-sulphonamide which was bacteriostatic against a wide range of Gram-positive and Gram-negative organisms only at concentrations greater than 1 in 1000; also Dr. S. R. M. Bushby of the Wellcome Research Laboratories for the preliminary bacteriological examination of the derivatives of pyridine-4-sulphonhydrazide listed in Tables 1 and 2: against *Myco. tuberculosis* var. hominis (CN3679) both in Dubos and Davies's medium [13] and in the egg-agar solid medium of Peizer and Schecter,[14] none showed significant activity.

Experimental

We thank Mr. W. McCorkindale and Dr. A. C. Syme for the microanalyses.

Pyridine-4-sulphonamide.—(*a*) 4-Pyridthione (1·11 g.) in concentrated hydrochloric acid (7·5 ml.) and water (2 ml.), cooled to −10°, was chlorinated at such a rate as to keep the temperature at about −5°. After the end of chlorination, the mixture was poured on ice (15 g.), and the slurry transferred to ice-cold ammonia (40 ml.; *d* 0·88). The mixture was kept at room temperature for 3 hr., then concentrated in a vacuum until solid began to separate, and next cooled at 0° overnight; it yielded *pyridine-4-sulphonamide* as rhombic prisms (0·91 g., 58%), m. p. 172—173° (from ethanol or water) (Found: C, 38·3; H, 3·5; N, 17·5. $C_5H_6O_2N_2S$ requires C, 38·0; H, 3·8; N, 17·7%).

(*b*) 4-Pyridthione (1·11 g.) was chlorinated as in (*a*), and the solution was treated with calcium carbonate (*ca.* 1 g. to part-neutralise acid and displace dissolved chlorine) and poured into ice-cold chloroform (20 ml.). Calcium carbonate (*ca.* 7 g.) was carefully added, with shaking, at −5°, to complete the neutralisation. After being shaken vigorously the clear chloroform solution was decanted from the almost solid white sludge, which was then washed further with cold chloroform (2 × 20 ml.). The combined chloroform solutions were dried (Na_2SO_4) at 0—5° and filtered, and dry ammonia gas passed into the filtrate for 10 min. After cooling, the precipitated product (0·93 g., 60%) was filtered off and recrystallised, to yield pyridine-4-sulphonamide, m. p. 172—173° (from water). Its *picrate* (plates) had m. p. 186—187° (decomp.) (from ethanol) (Found: C, 34·3; H, 1·9; N, 17·9. $C_{11}H_9O_9N_5S$ requires C, 34·1; H, 2·3; N, 18·0%).

Pyridine-4-sulphonamide 1-*Oxide.*—Pyridine-4-sulphonamide (0·158 g.) was heated with 30%

[10] Fox and Gibas, *J. Org. Chem.*, 1953, **18**, 1375.
[11] Dann and Davies, *J.*, 1929, 1050.
[12] Carpino, *J. Amer. Chem. Soc.*, 1957, **79**, 4427.
[13] Dubos and Davies, *J. Exp. Med.*, 1946, **83**, 409.
[14] Peizer and Schecter, *Amer. J. Clin. Path.*, 1950, **20**, 682.

hydrogen peroxide (0·3 ml.) and glacial acetic acid (0·4 ml.) at 70—80° for 5 hr. Concentration in a vacuum gave a brown solid (0·085 g., 49%) which recrystallised from ethanol (5 ml.; charcoal) to yield pyridine-4-sulphonamide 1-oxide, m. p. 230° (decomp.). Naito and Dohmori [4] give m. p. 228°.

Pyridine-4-sulphonanilide.—4-Pyridthione (1·11 g., 0·01 mole) was converted into pyridine-4-sulphonyl chloride as in (*b*), and the cold, dry chloroform solution of the latter shaken with aniline (1·86 g., 0·02 mole), left overnight at 0°, filtered, and evaporated under reduced pressure. The residual oil recrystallised from methanol (60%) as needles (1·48 g., 65%) of *pyridine-4-sulphonanilide*, m. p. 135—136° (Found: N, 12·1. $C_{11}H_{10}O_2N_2S$ requires N, 12·0%).

Pyridine-4-sulphonhydrazide.—Batches of 4-pyridthione (5·55 g., 0·05 mole) were chlorinated as in (*b*) above. Addition of the cold, dry chloroform solution of pyridine-4-sulphonyl chloride in 10—20 ml. portions to anhydrous hydrazine (3·2 g., 0·1 mole) with shaking caused deposition of colourless crystals. The mixture was left overnight at 0°, then filtered, and the residue was washed with ether and dried *in vacuo*. The crude product was suspended in ice-cold water (15 ml.), quickly filtered, washed with ice-cold water (5 × 1 ml.), and dried *in vacuo* (sulphuric acid), yielding *pyridine-4-sulphonhydrazide* (6·3 g., 73%) as needles, m. p. 95—96° (from ice-cold water or methanol) (Found: C, 35·0; H, 3·7; N, 24·5; S, 18·2. $C_5H_7O_2N_3S$ requires C, 34·7; H, 4·1; N, 24·3; S, 18·5%). It gave a *picrate* (from ethanol), m. p. 117—118° (Found: C, 32·9; H, 2·31; N, 20·7. $C_{11}H_{10}O_9N_6S$ requires C, 32·8; H, 2·5; N, 20·9%), *dihydrochloride* (from methanol), m. p. 122—123° (Found: C, 25·7; H, 4·8; S, 11·7. $C_5H_9O_2N_3Cl_2S,CH_3{\cdot}OH$ requires C, 25·9; H, 4·7; S, 11·5%), and *sodio-derivative* (by treatment with sodium ethoxide), m. p. *ca.* 285° (Found: C, 30·3; H, 3·8; Na, 11·8. $C_5H_6O_2N_3SNa$ requires C, 30·8; H, 3·1; Na, 11·8%). Pyridine-4-sulphonhydrazide is insoluble in benzene, ether, and chloroform, sparingly soluble in alcohol, and soluble in methanol and water. Aqueous solutions slowly become yellow with evolution of nitrogen, even at 0°; similar decomposition occurs in hot methanol. The solid slowly becomes yellow and a pyridine-like odour develops.

1-Alkylidene- and 1-Aralkylidene-2-pyridine-4′-sulphonylhydrazines.—Pyridine-4-sulphonhydrazide (0·865 g., 0·005 mole), suspended in methanol (5 ml.), was shaken with aldehyde or ketone (0·005 mole) and sufficient methanol to give a homogeneous solution. The crystalline *products* which separated (if necessary after concentration of the solution) recrystallised from ethanol, methanol, or mixtures of these with water. Constants and analyses are recorded in Table 1.

1-Ethylidene-2-pyridine-4′-sulphonylhydrazine picrate was obtained as needles (from ethanol), m. p. 113° (Found: C, 36·6; H, 2·4. $C_{13}H_{12}O_9N_6S$ requires C, 36·5; H, 2·8%). The *picrate* of the *iso*propylidene analogue formed prisms (from methanol), m. p. 135—136° (decomp.) (Found: C, 38·2; H, 3·1; N, 19·2. $C_{14}H_{14}O_9N_6S$ requires C, 38·0; H, 3·2; N, 19·0%), and that of the furfurylidene compound prisms (from ethanol), m. p. 161° (decomp.) (Found: C, 40·5; H, 2·2; N, 17·4. $C_{16}H_{12}O_{10}N_6S$ requires C, 40·0; H, 2·5; N, 17·5%).

1-Phenyl-2-pyridine-4′-sulphonylhydrazine.—4-Pyridthione (1·11 g., 0·01 mole) was converted into pyridine-4-sulphonyl chloride as before, and the cold dry chloroform solution of the latter shaken with phenylhydrazine (2·16 g., 0·02 mole) in chloroform (10 ml.), then left overnight at 0°; the product was separated, washed with chloroform, dried *in vacuo*, then washed free from chloride with ice-cold water, and recrystallised from ethanol to yield *1-phenyl-2-pyridine-4′-sulphonylhydrazine* (0·3 g., 12%), m. p. 145° (decomp.) (Found: N, 16·7. $C_{11}H_{11}O_2N_3S$ requires N, 16·9%).

1 : 1-*Diacetyl-2-pyridine-4′-sulphonylhydrazine.*—Pyridine-4-sulphonhydrazide (0·865 g.) was added in small portions to acetic anhydride (5 ml.), with shaking and gentle warming until complete solution was effected. On cooling, the *diacetyl compound* (0·96 g., 69%) separated as colourless prisms, m. p. 161° (decomp.) (Found: C, 42·1; H, 3·7; S, 12·4. $C_9H_{11}O_4N_3S$ requires C, 42·0; H, 4·3; S, 12·45%).

1-Acyl-2-pyridine-4′-sulphonylhydrazines.—Pyridine-4-sulphonhydrazide (0·865 g., 0·005 mole), suspended in methanol (5 ml.) or dry dioxan, was shaken with the acid anhydride (0·005 mole) and sufficient solvent to give a homogeneous solution. The crystalline products which separated were recrystallised from ethanol or methanol. Constants and analyses are in Table 2.

1-Benzoyl-2-pyridine-4′-sulphonylhydrazine hydrochloride had m. p. 194° (decomp.) (Found: C, 45·9; H, 3·7. $C_{12}H_{12}O_3N_3ClS$ requires C, 45·8; H, 3·9%).

1-Phenylcarbamoyl-2-pyridine-4′-sulphonylhydrazine.—Pyridine-4-sulphonhydrazide (0·865

g., 0·005 mole), suspended in methanol (5 ml.), was treated with phenyl *iso*cyanate (0·6 g.) in methanol (5 ml.). When shaken, the mixture became homogeneous and almost immediately deposited the *phenylcarbamoyl derivative* (1·2 g., 80%) as prisms, m. p. 200° (decomp.) (Found: N, 19·1. $C_{12}H_{12}O_3N_4S$ requires N, 19·2%).

1-*Allylthiocarbamoyl*-2-*pyridine*-4′-*sulphonylhydrazine*.—Pyridine-4-sulphonhydrazide (0·865 g., 0·005 mole), suspended in methanol (5 ml.), was treated with allyl *iso*thiocyanate (0·49 g.) in methanol (2 ml.). The *product* (0·35 g., 25%), which separated overnight at 0° and on subsequent concentration, was obtained as prisms, m. p. 149° (decomp.), from methanol (Found: N, 20·6. $C_9H_{12}O_2N_4S_2$ requires N, 20·6%).

1-*Benzenesulphonyl*-2-*pyridine*-4′-*sulphonylhydrazine*.—Pyridine-4-sulphonhydrazide (0·432 g., 0·0025 mole) was treated dropwise with benzenesulphonyl chloride (0·44 g., 0·0025 mole) in dry pyridine (5 ml.), with cooling, and stirred until solution was complete. Ice-cold water (15 ml.) was then slowly added, and the *product* collected and recrystallised as needles (0·31 g.) (from ethanol), m. p. 142—143° (decomp.) (see Table 2 for analytical data).

1-Pyridine-4′-sulphonyl-2-toluene-*p*-sulphonylhydrazine was prepared similarly.

1 : 2-*Di*(*pyridine*-4′-*sulphonyl*)*hydrazine*.—Pyridine-4-sulphonhydrazide (0·865 g.) in dry pyridine (10 ml.) was treated with pyridine-4-sulphonyl chloride [from 4-pyridthione (1 g.)] in chloroform, with cooling. The product which separated overnight at 5° was filtered off, washed with ether, suspended in water (10 ml.), filtered off, and dried *in vacuo*, to yield 1 : 2-*di*(*pyridine*-4′-*sulphonyl*)*hydrazine* (0·95 g.), m. p. 173—174° (decomp.) (from dimethylformamide–ethanol) (see Table 2).

3-*Methyl*-1-(*pyridine*-4′-*sulphonyl*)-5-*pyrazolone*.—Pyridine-4-sulphonhydrazide (0·173 g., 0·001 mole) in methanol (1 ml.) was shaken with ethyl acetoacetate (0·13 g., 0·001 mole) in methanol (1 ml.) and left overnight at 0°. The *pyrazolone* (0·18 g., 75%) was deposited as needles, m. p. 124—125° (from methanol) (Found: N, 17·7. $C_9H_9O_3N_3S$ requires N, 17·6%).

Benzyl 4-*Pyridyl Sulphone*.—Pyridine-4-sulphonhydrazide (0·865 g., 0·005 mole) was added in small amounts to sodium (0·23 g., 0·01 g.-atom) in ethanol (10 ml.), and benzyl chloride (1·28 g., 0·01 mole) was added rapidly before the monosodio-derivative separated. The solution was refluxed for 4 hr. on a water-bath, cooled, filtered to remove sodium chloride, and concentrated, to yield the *sulphone* (0·25 g.) in plates, m. p. 169—170° (decomp.) (from aqueous methanol) (Found: C, 61·2; H, 4·6; N, 6·1. $C_{12}H_{11}O_2NS$ requires C, 61·8; H, 4·7; N, 6·0%).

Reaction of Pyridine-4-*Sulphonamide with Hydrazine*.—(*a*) Pyridine-4-sulphonamide (0·79 g.) was heated with anhydrous hydrazine (0·9 g.) on a boiling-water bath for 30 min. After a few minutes the mixture separated into two layers, but it became homogeneous on further heating, with evolution of ammonia and gentle intermittent bubbling. Evaporation under reduced pressure gave colourless needles (0·7 g.), m. p. 161° (decomp.) (from methanol) (Found: C, 24·8; H, 5·4; N, 24·0. $C_5H_{12}O_3N_4S_2$ requires C, 25·0; H, 5·0; N, 23·3%). The product, probably *ammonium* 4-*pyridylhydrazinium thiosulphate*, when treated with dilute hydrochloric acid, liberated sulphur dioxide and colloidal sulphur; extraction of the latter with carbon disulphide and evaporation of the aqueous solution gave 4-pyridylhydrazine hydrochloride, m. p. 241° (decomp.) (from ethanol). Koenigs, Weiss, and Zscharn [15] give m. p. 238°. An aqueous solution of the product gave a white precipitate with lead acetate (Found: Pb, 65·9. PbS_2O_3 requires Pb, 64·9%). With sodium hydroxide no ammonia could be detected, but an oil insoluble in the common organic solvents was produced, and on exposure to air a deep pink colour developed. 4-Pyridylhydrazine beomes pink in air.

(*b*) Pyridine-4-sulphonamide (0·79 g.) and anhydrous hydrazine (0·16 g.) in methanol (10 ml.) were refluxed until no more ammonia was evolved (*ca.* 7 hr.). Cooling and storage for 3 days gave a product (0·62 g.), identical with that obtained in (*a*). Concentration of the mother-liquors gave a yellow substance (0·2 g.), m. p. 130—170° which on repeated crystallisation from methanol yielded 4-*pyridylhydrazinium pyridine*-4′-*sulphonate*, m. p. 226—227° (decomp.) (Found: C, 44·3; H, 4·2; N, 20·7. $C_{10}H_{13}O_3N_4S$ requires C, 44·8; H, 4·5; N, 20·9%). An aqueous solution passed through a column of Deacidite FF gave an eluate, which, on acidification with dilute hydrochloric acid and evaporation, yielded 4-pyridylhydrazine hydrochloride, m. p. 241° (decomp.) (from aqueous ethanol).

THE SCHOOL OF PHARMACY, THE ROYAL COLLEGE OF SCIENCE AND TECHNOLOGY, GLASGOW.

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[15] Koenigs, Weiss, and Zscharn, *Ber.*, 1926, **59**, 316.

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709. *Mannose-containing Polysaccharides. Part V.* The Isolation of Oligosaccharides from Lucerne and Fenugreek Galactomannans.*

By (Miss) Margaret E. Henderson, L. Hough, and T. J. Painter.

Partial acid hydrolysates of the galactomannans of lucerne and fenugreek seeds have afforded in each case 4-*O*-β-D-mannopyranosyl-D-mannose, 6-*O*-α-D-galactopyranosyl-D-mannose, and *O*-β-D-mannopyranosyl-(1 → 4)-*O*-β-D-mannopyranosyl-(1 → 4)-D-mannose. Sucrose and raffinose were found in lucerne seed.

The endosperms of fenugreek and lucerne seeds contain mucilaginous galactomannans which were investigated by Andrews, Hough, and Jones.[1] Results obtained by exhaustive methylation and by periodate oxidation were consistent with a polymer structure involving a chain or backbone of β-1 → 4-D-mannopyranosyl units with D-galactopyranosyl units in attachment at various intervals through their reducing group to $C_{(6)}$ of mannose units. The identification of di- and tri-saccharides produced on partial hydrolysis of these galactomannans is described herein and fully confirms these structural findings.

During the acid hydrolysis of the galactomannans, the liberation was observed first of galactose alone, followed by a mixture of mono- and oligo-saccharides. The oligosaccharides from fenugreek galactomannan were fractionated by adsorption on a column [2] of charcoal–Celite, followed by elution with water, the addition of a displacing agent such as ethanol being unnecessary. Of the oligosaccharides, mannobiose appeared in the effluent first, followed by 6-*O*-α-D-galactopyranosyl-D-mannose and then by mannotriose. The mannobiose and mannotriose were identical with 4-*O*-β-D-mannopyranosyl-D-mannose and *O*-β-D-mannopyranosyl-(1 → 4)-*O*-β-D-mannopyranosyl-(1 → 4)-D-mannose trihydrate isolated by Aspinall, Rashbrook, and Kessler [3] from the mannans of ivory nut.

Examination of the mannobiose by oxidation with sodium metaperiodate under unbuffered conditions and also at pH 3·6 revealed that the reducing unit of the disaccharide reacted in the pyranose form with the formation of a relatively stable formyl ester. The slow breakdown of this ester has been attributed to the presence of the 1 : 4-linkage within the molecule, so preventing the formation of an electrophilic aldehyde group on the carbon atom adjacent to the ester linkage, which, in its presence, is labile.[4]

Partial hydrolysis of lucerne galactomannan gave similar results. Fractionation of the oligosaccharides on an acid-treated, charcoal–Celite column,[5] by gradient elution with water–ethanol, led to the isolation of crystalline 4-*O*-β-D-mannopyranosyl-D-mannose, *O*-β-D-mannopyranosyl-(1 → 4)-β-D-mannopyranosyl-(1 → 4)-D-mannose trihydrate, and 6-*O*-α-D-galactopyranosyl-D-mannose.

Exhaustive extraction of lucerne seed with methanol afforded a mixture of several oligosaccharides which was separated by chromatography on a cellulose column. Sucrose and raffinose [*O*-α-D-galactopyranosyl-(1 → 6)-*O*-α-D-glucopyranosyl(1 → 2)-β-D-fructofuranoside] were characterised, thus suggesting a plausible pathway whereby the galactomannan is synthesised and metabolised as a result of trans-glycosidation of D-galactopyranosyl units, in the first case from raffinose to a mannose polymer and in the second from the galactomannan to sucrose.

Experimental

Paper chromatography was carried out on Whatman No. 1 filter paper by the descending method with the following solvent systems: (*a*) butan-1-ol–ethanol–water (40 : 11 : 19 v/v);

* Part IV, *J.*, 1956, 181.

[1] Andrews, Hough, and Jones, *J.*, 1952, 2744.
[2] Whistler and Durso, *J. Amer. Chem. Soc.*, 1951, **73**, 4189.
[3] Aspinall, Rashbrook, and Kessler, *J.*, 1958, 215.
[4] Hough, Taylor, Thomas, and Woods, *J.*, 1958, 1212.
[5] Alm, Williams, and Tiselius, *Acta Chem. Scand.*, 1952, **6**, 826.

(*b*) ethyl acetate–acetic acid–water (9 : 2 : 2 v/v); (*c*) butan-1-ol–pyridine–water (10 : 3 : 3 v/v); (*d*) propan-1-ol–ethyl acetate–water (7 : 1 : 3 v/v). After separation, reducing sugars were located with *p*-anisidine hydrochloride.[6] Solutions were concentrated under reduced pressure. Optical rotations were observed at 20°, for aqueous solutions.

Selective Hydrolysis of Fenugreek Galactomannan.—The galactomannan (300 g. wet ≡ 68 g. dry) was prepared from milled fenugreek seeds (750 g.) as described previously [1] (Found: sulphated ash, 0·8; N, 0·3%). The polysaccharide was stored in a hydrated condition since it remained more soluble in this form. Preliminary experiments were carried out in order to determine the optimum conditions for di- and tri-saccharide formation. The polysaccharide (≡ 3 g. dry) was suspended in water (120 ml.) by vigorous shaking and heated at 80° ± 1° for 20 hr. in order to ensure complete dispersion. 5N-Hydrochloric acid (30 ml.) was then added with shaking and the heating continued. At hourly intervals two aliquot samples (5 ml. each) were withdrawn simultaneously and examined as follows.

One sample was neutralised with silver carbonate and filtered; hydrogen sulphide was passed through the filtrate, and the solution decolorised with charcoal: any absorbed sugar was eluted from the charcoal with aqueous ethanol. The solution was concentrated and examined on paper chromatograms [solvents (*b*), (*c*), and (*d*)]. During the hydrolysis, galactose appeared first (1 hr.), followed by mannose (2—3 hr.), and then at least six oligosaccharides were clearly distinguishable (3—4 hr.) which gradually disappeared leaving only monosaccharides (6 hr.).

The other sample was neutralised with 0·5N-sodium hydrogen carbonate and to this solution phosphate buffer (20 ml.; pH 11·6 at 25°) and *ca.* 0·1N-iodine (10—30 ml. depending on the reducing power) were added. After sealing with a stopper wetted with potassium iodide solution, the oxidation was allowed to proceed for 48 hr. when after the stopper had been washed the solution was acidified with dilute sulphuric acid and the liberated iodine was titrated with 0·05N-sodium thiosulphate. A control determination was carried out on a sample of the reaction mixture which had not been heated with acid. The results obtained for the increase in reducing power, expressed as aldohexose %, during hydrolysis were 5·85 (1 hr.), 22·9 (2 hr.), 29·6 (3 hr.), 37·3 (4 hr.), and 48·1 (5 hr.).

For the preparation of oligosaccharides, the galactomannan (226 g. ≡ 51 g. dry) was hydrolysed as described above at 80° for 3¼ hr., then the mixture was neutralised with sodium hydrogen carbonate and concentrated to *ca.* 300 ml.; any sodium chloride which had separated was filtered off.

Separation of the Oligosaccharides.—The neutral hydrolysate was passed into a column [2] (120 × 5 cm.) containing a wet mixture of B.D.H. acid-washed charcoal (200 g.) and Celite (200 g.), and elution carried out with water. The effluent from the column was collected in successive portions (*ca.* 100 ml.) which were concentrated and examined on paper chromatograms [solvent (*d*)]; appropriate fractions were combined. Some fractions contained small amounts of charcoal and Celite which were removed either by filtration through Whatman No. 42 paper or on the high-speed centrifuge. Paper chromatography indicated that mannose and galactose were first eluted, followed by two disaccharides (fractions *A* and *B*), a trisaccharide (fraction *C*), and then higher saccharides.

4-O-β-D-*Mannopyranosyl*-D-*mannose.* Fraction *A* was a crisp solid {0·28 g.; $[\alpha]_D$ −9·0° (*c* 1·38)} indistinguishable on paper chromatograms from authentic mannobiose, kindly provided by Dr. G. O. Aspinall. Paper chromatography of a hydrolysate of a small portion showed the presence of mannose only.

Attempts to crystallise the mannobiose from butan-1-ol–ethanol–water failed [cf. Whistler and Durso [2]], but after 8—9 months crystals were obtained which had m. p. and mixed m. p. 192—193°. The phenylosazone was prepared by heating a solution of the mannobiose (50 mg.) in water (2·8 ml.) and acetic acid (0·2 ml.) with phenylhydrazine (0·2 ml.) at 95—100° for 1 hr. After being washed with water and then with benzene, the yellow crystals were dried at 60° under reduced pressure and recrystallised from alcohol–benzene. Calculation [7] of the molecular weight of the phenylosazone from the absorption at 395 mμ gave a value of 515 (calc. for mannobiose phenylosazone: *M*, 520).

Oxidation of mannobiose (0·069 g.) with 0·3M-sodium metaperiodate (10 ml.) in water (made up to 50 ml.) was followed by determining at various intervals of time, the formic acid

[6] Hough, Jones, and Wadman, *J.*, 1950, 1702.
[7] Barry, McCormick, and Mitchell, *J.*, 1955, 222.

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liberated [8] and the uptake of oxidant (acid–thiosulphate method [9]). The respective values rose from 2·28 mol. (2 days) to 2·98 mol. (5 days) and from 4·2 mol. (2 days) to 4·75 mol. (5 days). In acetate buffer (pH 3·7) mannobiose rapidly consumed 4 mol. of periodate in 2—3 hr., further oxidation being comparatively slow.

6-O-α-D-*Galactopyranosyl*-D-*mannose*. Fraction *B* was a crisp solid (0·08 g.), a portion of which on hydrolysis with 2N-sulphuric acid for 1 hr. in an autoclave gave galactose and mannose. Crystallisation from butan-1-ol–ethanol–water gave 6-*O*-α-D-galactopyranosyl-D-mannose, m. p. and mixed m. p. 203°, $[\alpha]_D$ +120° (*c* 1·0) (Found: C, 41·5; H, 6·4. Calc. for $C_{12}H_{22}O_{11}$: C, 42·1; H, 6·4%). The disaccharide reacted with 5·97 mol. of sodium metaperiodate during 1 day and yielded 4·98 mol. of formic acid.

O-β-D-*Mannopyranosyl*-(1 ⟶ 4)-O-β-D-*mannopyranosyl*-(1 ⟶ 4)-D-*mannose trihydrate*. Fraction *C* (0·042 g.) was purified by chromatography on a cellulose column with 50% ethanol as the mobile phase, to give a syrup which slowly crystallised from 80% methanol. After recrystallisation from 50% ethanol, the mannotriose had m. p. 163—165° and mixed m. p. 167°, $[\alpha]_D$ −16° (*c* 0·2; initial value), and gave an *X*-ray powder photograph which was identical with that of an authentic specimen kindly provided by Dr. G. O. Aspinall (Found: H_2O, 9·4. Calc. for $C_{18}H_{32}O_{16}.3H_2O$: H_2O, 9·7%). Whistler and Smith [10] report m. p. 137—137·5° and $[\alpha]_D^{25}$ −24·7° ⟶ −23·3°, and Aspinall, Rashbrook, and Kessler [3] quote m. p. 134·5—135·5° (rapid heating), 166·5—169·5° (slow heating), $[\alpha]_D$ −15·7° ⟶ −20·2°.

Selective Hydrolysis of Lucerne Galactomannan.—The polysaccharide was prepared from powdered lucerne seeds (200 g.) as previously described and dried over phosphoric oxide under reduced pressure (yield, 9 g.). The galactomannan was hygroscopic, absorbing moisture from the atmosphere to the extent of 30% of its own weight. A hydrolysate of a 2% solution of the polysaccharide in 0·1N-hydrochloric acid at 60° was examined at various intervals of time on paper chromatograms. During the first hour, only galactose was detected, after which mannose and oligosaccharides appeared concurrently.

In a typical preparation of oligosaccharides, the galactomannan (5 g.) was hydrolysed at 80° in N-hydrochloric acid (50 ml.) for 3·5 hr. as described above. The mixture was then neutralised by passing through a column of Amberlite resin IR-4B (OH) and evaporated to a syrup.

Separation of the Oligosaccharides.—A solution of the syrup in water (10 ml.) was allowed to soak into a column (50 × 2·8 cm.) containing a wet mixture of B.D.H. decolorising charcoal (40 g.) and Celite (40 g.) which had been treated [5] previously with 6N-hydrochloric acid at 100° for 3 hr. and washed with water until free from acid. Gradient elution with water containing increasing amounts of ethanol was then carried out, and the effluent collected in 5 ml. portions on an automatic fraction-collector; 100 ml. of effluent represented an increment of 2·5% (v/v) in the ethanolic content of the eluate. After examination on paper chromatograms, the appropriate fractions were combined and concentrated in the presence of a little ammonia as the concentrates were apt to become acidic.

4-O-β-D-*Mannopyranosyl*-D-*mannose*. The first fraction {0·09 g.; $[\alpha]_D$ −4 4° (*c*, 1·5); R_{Gal} 0·64 (solvent *b*)} gave only mannose on hydrolysis of a small portion. On oxidation with sodium metaperiodate in the dark, 2·93 mol. of formic acid were released with the consumption of 5·06 mol. of oxidant (constant value) per mol. of mannobiose. In a similar oxidation at pH 3·6 (acetate buffer), 4·07 mol. of periodate reacted. The mannobiose crystallised on concentration of a solution in hot butanol–ethanol–water, and had m. p. and mixed m. p. 192—193°.

6-O-α-D-*Galactopyranosyl*-D-*mannose*. The second fraction {0·11 g.; $[\alpha]_D$ +123° (*c* 1·5); R_{Gal} 0·55 (solvent *b*)} was crystallised by concentration of a solution in methyl Cellosolve–methanol–water and had m. p. and mixed m. p. 202°, $[\alpha]_D$ +122·5 ⟶ 122·1 (*c* 1·0; 50 hr.). The derived phenylosazone had m. p. 170°, undepressed on admixture with that prepared from melibiose. Oxidation of the disaccharide with periodate required 40 hr. for complete reaction, when 6·04 mol. of oxidant had reacted and 5·03 mol. of formic acid were liberated.

An unidentified trisaccharide. The third fraction {0·13 g.; $[\alpha]_D$ +32·5° (*c* 3·0); R_{Gal} 0·37 (solvent *b*)} contained galactose (1 mol.) and mannose (2 mol.) as revealed by separation of a hydrolysate of a small portion by paper chromatography followed by determination of the separated monosaccharides by oxidation with alkaline solution of iodine.[1]

O-β-D-*Mannopyranosyl*-(1 ⟶ 4)-O-β-D-*mannopyranosyl*-(1 ⟶ 4)-D-*mannose trihydrate*.

[8] Halsall, Hirst, and Jones, 1947, 1427.
[9] Hughes and Nevell, *Trans. Faraday Soc.*, 1948, **44**, 941.
[10] Whistler and Smith, *J. Amer. Chem. Soc.*, 1952, **74**, 3795.

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The fourth fraction {0·11 g.; $[\alpha]_D$ −22° (*c* 0·72); R_{Gal} 0·31 (solvent *b*)} was indistinguishable from mannotriose on paper chromatograms. Concentration of a solution in propanol–water gave crystals with m. p. and mixed m. p. 167°.

Sucrose and Raffinose from Lucerne Seed.—The milled seed (150 g.) was continuously extracted with methanol (500 ml.) for 36 hr. On evaporation the extract yielded a dark brown syrup which was washed with several portions of benzene, then dissolved in methanol (250 ml.) and decolorised (charcoal). The syrup (12 g.) obtained on evaporation of the solvent contained several oligosaccharides [R_{Gal} 0·88, 0·54, 0·29 (solvent *d*)] as revealed by paper chromatography. Separation of the mixture on a cellulose column,[6] with solvent *a*, gave sucrose (0·65 g.), m. p. and mixed m. p. 180—181°, and raffinose (0·23 g.), m. p. and mixed m. p. 78°, $[\alpha]_D$ +105° (*c*, 1·61).

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710. *Radiation Chemistry of Carbohydrates. Part I. Action of Ionising Radiation on Aqueous Solutions of* D-*Glucose.*

By G. O. PHILLIPS, G. J. MOODY, and (in part) G. L. MATTOK.

When irradiated in dilute aqueous solution, D-glucose is degraded to D-glucuronic acid, D-gluconic acid, glyoxal, D-arabinose, D-erythrose, formaldehyde, saccharic acid, and 1 : 3-dihydroxyacetone, which have been estimated quantitatively. Hydrogen peroxide is also formed.

Under fully oxygenated and evacuated conditions, variation in glucose concentration and dose rate does not influence the yield of acid; the extent and pattern of degradation are the same for 1 Mv electrons and cobalt gamma-radiation.

The liberation of gas indicates a post-irradiation process, also shown by changes in ultraviolet absorption spectra and hydrogen peroxide concentration.

The absorption spectrum of the irradiated solutions shows a characteristic absorption maximum at 265 mμ, sensitive to alkali; it is related to 1 : 3-dihydroxyacetone.

By following the yield–dose curves for the main products, the primary and secondary products are distinguished. The main types of degradation are thus identified.

ALTHOUGH the chemical action of ionising radiations on organic compounds has been widely studied, information regarding the behaviour of carbohydrates is meagre. Attention has been focused mainly on some of the physical changes observable during irradiation, such as pH, optical rotation, reducing power, viscosity and ultraviolet absorption spectra.[1,2] In a preliminary study we found that an aqueous solution of D-glucose after irradiation with fast electrons shows an absorption band at 200—300 mμ, and that glucuronic acid is formed.[3] Our subsequent investigations, however, revealed several other products. Bothner-By and Balazs [2] recently reported that solutions of the sugar irradiated with *X*-rays at doses ranging from 1 to 10^7 rads show an absorption band in this range; although no products were identified they state that glucuronic acid was not formed. In the present work we have examined the behaviour of aqueous solutions

[1] Holtz and Becker, *Arch. Expt. Pathol. Pharmakol.*, 1936, **182**, 160; Holtz, *ibid.*, 1936, **182**, 141; Slosse, *Compt. rend. Soc. Biol.*, 1923, **89**, 96; Kertesz, Bruce, Tuttle, and Lavin, *Radiation Res.*, 1956, **5**, 372.

[2] Bothner-By and Balazs, *Radiation Res.*, 1957, **6**, 302.

[3] Phillips, *Nature*, 1954, **173**, 1044.

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of D-glucose under evacuated and fully oxygenated conditions when irradiated with 1 Mv electrons and with gamma radiation.

Experimental

Electron Beam.—The irradiations were carried out with a beam of high-energy electrons from the 2 Mv van de Graaf Generator of the Chemistry Division, A.E.R.E., Harwell. The vertical electron beam accelerated to 1·25 Mv was turned through 90° by means of a magnet, and directed into the cell through a graphite collimator. This arrangement reduced stray radiation effects and ensured that the main electron beam entered the cell without impinging on the glass sides. The cell was placed 3 cm. from the aluminium window of the generator. The cells [4] were provided with windows of thin Pyrex glass to minimise energy losses. One type of window weighed 100 mg./cm.,[2] corresponding to a threshold voltage of the order of 0·24 Mv. The other type was much thinner (30 mg./cm.[2]), and the energy loss was only 0·07 Mv.[5] A well containing mercury permitted connection between the charge-collecting lead (through a platinum–tungsten lead sealed in the cell wall) and the current-collecting lead from the measuring instrument. The volumes of the cells ranged from 10 to 11 ml. Irradiation times could be reduced to 10 sec. by means of a beam interrupter,[6] and cell currents ranging from 0·01 to 1·0 μA were employed, corresponding respectively to energy-input rates of $3{\cdot}7 \times 10^{18}$—$3{\cdot}7 \times 10^{20}$ ev/min. Energy-input rates were calculated directly from the beam voltage and current within the cell and refer to a total volume of 10 ml. The current in the platinum wire within the cell was led along a shielded lead to earth through a D.C. amplifier and current integrator which would take into account any variation in cell current. Since the currents measured were small, it was necessary to ensure that the leakage resistance of the current-carrying lead to earth was high. The generating voltmeter measured the beam voltage directly, and a correction for energy losses in the cell window was applied as described.

Electron-beam Irradiation of Glucose Solutions.—A de-oxygenated solution (10 ml.) of D-glucose (5·5 millimoles) was irradiated with electrons (1 Mv) at 1 μA for 1 hr. (energy-input rate $3{\cdot}75 \times 10^{20}$ ev/min.); the pH fell to 3·25, and $[\alpha]_D$ from +51·6° to +0·14°. At this high dose rate similar behaviour was shown by the air-equilibrated solution, because the depletion of oxygen in the vicinity of the beam is faster than its diffusion from the body of the solution. The distillate obtained by heating the solution below 40° under reduced pressure contained a trace of acid, but did not form a complex with dimedone or *p*-bromoformanilide. Paper chromatography with butan-1-ol–pyridine–water, followed by spraying with aniline hydrogen phthalate and silver nitrate, gave highly streaked chromatograms, but with practice it was possible to identify three spots corresponding to glucose (R_F 0·37), glucuronic acid (R_F 0·07), and glucurone (R_F 0·66).

In another experiment, [^{14}C]glucose (generally labelled) (100 μc) was added to the original solution, and the mixture irradiated. The autoradiograph (24 hr.) was identical in pattern with the chromatogram obtained with the spray reagent.

Rate of Acid Formation in the Absence of Oxygen.—The concentration of acid increased linearly with energy input (Fig. 1). The yield was independent of the initial glucose concentration in the range $5{\cdot}5 \times 10^{-2}$ to $5{\cdot}5 \times 10^{-3}$M, and of the energy absorption in the range $3{\cdot}75 \times 10^{20}$ to $3{\cdot}75 \times 10^{19}$ ev. By assuming that the acid is monobasic, it was found that G(acid) = 0·41.

Evolution of Gas.—The cell employed for investigating the evolution of gas on irradiation [4] was provided with a mercury bellows-manometer [7] and a break-seal for use when gas is pumped off. The cell was charged with the glucose solution, and the system freed from air by the freeze-pump technique before irradiation. During irradiation the cell was maintained at the selected temperature within ±0·05°. After irradiation of the solution, the gases were removed at −196° and the residual volatile material at −90°. The gases were measured in a calibrated Töpler pump before analysis.

An evacuated glucose solution (5×10^{-2}M) on irradiation at 30° with 1 Mv electrons at an energy input of $3{\cdot}75 \times 10^{20}$ ev/min. evolved gas at the rate of 0·114 ml./min. The pressure in

[4] Amphlett and Williams, *J. Sci. Instr.*, 1956, **33**, 64.
[5] Williams and Wilkinson, *J. Chim. phys.*, 1955, **52**, 600.
[6] Miller, A.E.R.E. C/R. 1068.
[7] Spence, *Trans. Faraday Soc.*, 1940, **36**, 417.

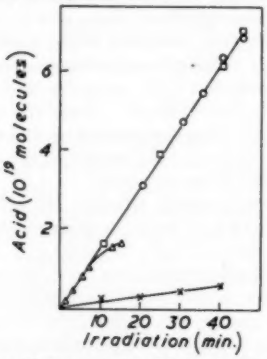
the cell increased linearly with energy input (Fig. 2). After irradiation, the evolution continued for 30 hr. Of the total gas (8·5 ml.), the part gaseous at −196° consisted of hydrogen (98%) and carbon monoxide (2%), while the part gaseous at −90° (0·9 ml.) contained about 90% of carbon dioxide. Experiments at 30° and 40° are reported in Table 1.

TABLE 1. *Irradiation of glucose solutions with* 1 Mv *electrons* (*energy input* $3{\cdot}25 \times 10^{20}$ ev/*min.*).

Temp.	Time (min.)	G (total gas)	Post-irradiation evolution (%)
30°	66	1·1	24
40	60	1·1	20

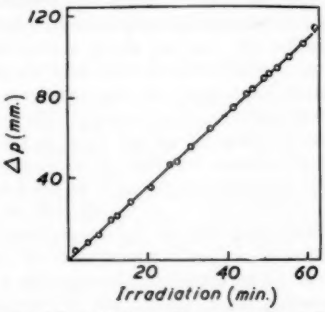
Acid Yield under Oxygenated Conditions.—Owing to the depletion of oxygen in the vicinity of the electron beam (1 μA and energy input of $3{\cdot}75 \times 10^{20}$ ev/min.), the passage of oxygen through the irradiated glucose solution did not affect the yield of acid. For measurements of acid yield under fully oxygenated conditions, we employed lower dose rates with beam current

FIG. 1. *Acid production during irradiation of aqueous* D-*glucose with* 1 Mv *electrons.*



□ $5{\cdot}5 \times 10^{-3}$M, ○ $5{\cdot}5 \times 10^{-2}$M, Δ $5{\cdot}5 \times 10^{-3}$M (*energy input* $3{\cdot}75 \times 10^{20}$ ev/min.); × $5{\cdot}5 \times 10^{-3}$M (*energy input* $3{\cdot}75 \times 10^{19}$ ev/*min.*)

FIG. 2. *Gas evolution during irradiation of evacuated* D-*glucose solutions with* 1 Mv *electrons.*



Glucose $5{\cdot}5 \times 10^{-2}$M. *Energy input* $3{\cdot}75 \times 10^{20}$ ev/*min. Temp.* 30°.

varying from 0·01 to 0·05 μA. The results for glucose solutions (10^{-2}—10^{-3}M) are shown in Fig. 3. The rate of formation of acid increases gradually with dose, and the initial rate corresponds to G(acid) 1·2—1·3, on the assumption that the acid formed is monobasic.

Absorption Spectrum of Irradiated Solutions.—A typical absorption spectrum of an irradiated glucose solution is shown in Fig. 4. Further evidence of a slow post-irradiation reaction was furnished by the change in the ultraviolet spectrum of the irradiated solution. The absorption at 265 mμ (Fig. 4) increased steadily and attained a maximum 20—30 hr. after irradiation had ceased. The addition of potassium hydrogen carbonate led to a sharp increase in the absorption in this region.

Action of Gamma Radiation.—Gamma radiation was provided by a cobalt-60 source (200 curies) similar in design to that developed at A.E.R.E., Harwell, and described by Gibson and Pearce,[8] and varying dose rates were obtained by arranging the irradiation vessels at different distances from the source.

The chemical method employed for dosimetry was based on the oxidation of ferrous sulphate in highly purified water,[9] the solution being 10^{-3}M in ferrous ion and 0·8N in sulphuric acid. The concentration of ferric ion was determined by means of a Unicam S.P. 500 spectrophotometer: max. 301 mμ, ε 2050, and $G(Fe^{3+})$ was taken as 15·5. Addition of inorganic ions (KCl 10^{-2}M) had no effect on the yield.

Where maximum energy deposition into the solution was required, glass cells with a central

[8] Gibson and Pearce, *Chem. and Ind.*, 1957, 613.
[9] Amphlett, *Discuss. Faraday Soc.*, 1952, **12**, 145.

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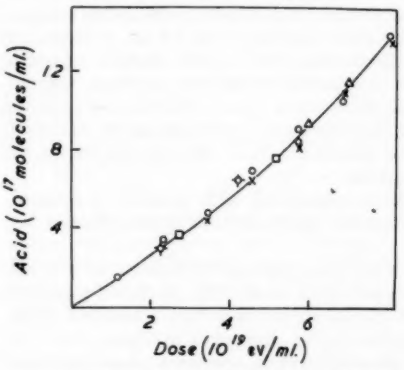
annulus, into which the source could be inserted, were used. In this type of cell volumes of 100—150 ml. were irradiated. For lower dose rates, glass cells (*ca.* 40 ml.) fitted with a sintered disc for oxygenation were placed around the source on a turn-table (4 revs./3 min.) to ensure even and reproducible dose rates. During the irradiations, the system was either de-aerated on a high-vacuum line or saturated with oxygen by passing the gas through a sintered disc into the solution. The dose rates into the annular cells were $2{\cdot}13 \times 10^{17}$ ev min.$^{-1}$ ml.$^{-1}$ and into the smaller cells $9{\cdot}65 \times 10^{16}$ ev min.$^{-1}$ ml.$^{-1}$.

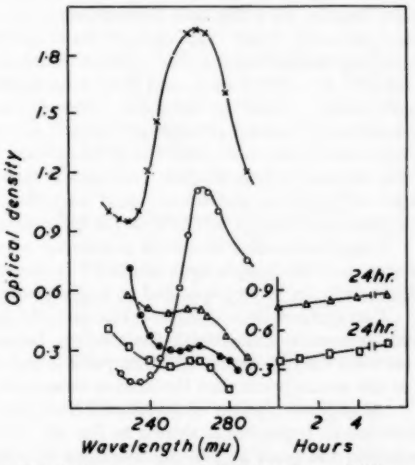
Chromatography.—The constituents in the irradiated glucose solution were separated chromatographically on Whatman paper No. 1. The free sugars were irrigated with butan-1-ol–acetic acid–water (4 : 1 : 5), and detected with *p*-anisidine hydrochloride, aniline hydrogen phthalate, or silver nitrate.[10] Osazones were separated by the circular paper method [11] with toluene–ethanol–water (9 : 1 : 1) and detected with ammoniacal silver nitrate. Anilides were separated with benzene–acetone–water (2 : 9 : 1) containing 0·01% of rhodanine and were detected by their fluorescence in ultraviolet light.[12] Lactones of the sugar acids were separated with butan-1-ol–ethanol–water (4 : 1 : 5) and detected by spraying with hydroxylamine in potassium hydroxide solution and then with dilute ferric chloride.[13] For the autoradiographic examination, known volumes of irradiated solutions of [^{14}C]glucose were applied to the paper and irrigated as described for 24—30 hr. The dried paper was placed in contact with Ilford "B" *X*-ray film in lead-backed holders, and satisfactory autoradiographs were obtained after 2—4 months.

FIG. 3. *Acid production during irradiation of* D-*glucose solutions in oxygen.*



	Electron beam (μA)	Energy input (10^{19} ev/min.)	Glucose concn. (10^{-3}M)
⊹	0·02	0·74	50
△	0·05	1·85	50
□	0·05	1·85	5
	^{60}Co γ radn.		
○	—	0·38	50
×	—	0·38	5

FIG. 4. *Ultraviolet absorption spectra of irradiated* D-*glucose solutions.*



1 Mv *electrons, energy input* (Δ) $2{\cdot}4 \times 10^{22}$ ev, (×) $2{\cdot}4 \times 10^{22}$ ev (*aq.* $KHCO_3$ *added after irradiation*), (□) 1×10^{22} ev, in vacuo, *vol.* 10 *ml., optical density* ÷ 4.
^{60}Co γ *radiation, energy input* (◐○) 8×10^{22} ev, (○ only) *aq.* $KHCO_3$ *added after irradiation*), *in* O_2 *vol.* 40 ml.
Inset: post-irradiation increase in optical density at 265 mμ.

Chromatographic Separation of Irradiation Products.—A solution (150 ml.) of D-glucose (5×10^{-2}M) was irradiated to total energy input $4{\cdot}6 \times 10^{22}$ ev and then chromatographed with butan-1-ol–acetic acid–water. Excessive streaking precluded the use of silver nitrate as a spray

[10] Hough, Jones, and Wadman, *J.*, 1950, 1702.
[11] Barry and Mitchell, *J.*, 1954, 4020.
[12] Green, *J. Amer. Chem. Soc.*, 1956, **78**, 1894.
[13] Abdel-Akher and Smith, *ibid.*, 1951, **73**, 3859.

reagent. Streaking was less marked with *p*-anisidine which revealed five spots: brown, R_F 0·18, glucose; pink, R_F 0·11, glucuronic acid; pink, R_F 0·34, glucuronolactone; pink, R_F 0·22; faint yellow, R_F 0·48. The relative sizes of the spots indicated that glucuronic acid was present mainly as the lactone.

A solution (150 ml.) of [^{14}C]glucose (5×10^{-2}M; 50 μc) was irradiated with energy input varying from $1{\cdot}9 \times 10^{21}$ to $4{\cdot}19 \times 10^{22}$ ev. After chromatography, the autoradiographs showed a spot (R_F 0·75) which was not revealed by the spray reagent.

The irradiated solution was treated with phenylhydrazine in acetic acid, and the solid phenylhydrazones were separated by circular paper chromatography.[11] This method indicated the presence of erythrosazone (R_F 0·52) and glyoxal bisphenylhydrazone (R_F 0·97) in addition to glucosazone (R_F 0·42).

The distillate from the irradiated solution contained a small amount of volatile acid, but gave no complex with dimedone. Gluconic and glucuronic acid in the irradiated solution were converted into anilides, which where chromatographed and identified in ultraviolet light: anilide of gluconic (R_F 0·52), and of glucuronic acid (R_F 0·36) We distinguished between the substance in the irradiated solution corresponding to glucuronic (pink, R_F 0·11), 5-oxogluconic acid (brown, R_F 0·28), and 2-oxogluconic acid (pink, R_F 0·14) by chromatography with butan-1-ol–acetic acid–water In view of the similarity between the first and the third acid, we applied a further distinguishing test The irradiated solution (0·5 ml.) was treated with iodine solution (4·0 ml., 3×10^{-2}M in I_2 and 0·1M in potassium iodide made alkaline with 0·4 ml. of N-sodium hydroxide). After 15 min. the solution was neutralised with solid carbon dioxide. Control solutions containing glucose, glucuronic acid, and the oxogluconic acids were similarly treated. Paper electrophoresis (550 v in 0·2M-acetate buffer of pH 5) for 6—8 hr., followed by spraying with alkaline silver nitrate, revealed a fast-running spot (brown) corresponding to saccharic acid in both the glucuronic acid and the irradiated solution. This was not shown by the untreated irradiated solution or the other control solutions.

The irradiated solution of D-glucose was also chromatographed with butan-1-ol–ethanol–water, and the purple spot (R_F 0·33) produced by successive spraying with hydroxylamine and ferric chloride [12] corresponded to D-glucurone.

Rate of Formation of Acid.—The rate of formation of acid in oxygenated solutions (40 ml.) was similar to that found with the electron beam. The yield–dose curve (Fig. 3) shows a gradual rise with energy input, and the yield is independent of concentration within a ten-fold range. On the assumption that the acid is monobasic, the initial slope corresponds to G(acid) 1·2—1·3.

Absorption Spectra of Irradiated Solutions.—A typical absorption spectrum of an irradiated solution of D-glucose is shown in Fig. 4. On addition of potassium hydrogen carbonate to the solution the peak at 265 mμ increases in intensity, and the minimum moves to 230 mμ. The compound responsible for the peak was formed throughout the irradiation and more rapidly in a vacuum than in oxygen (Fig. 5). Of the spectra represented in Fig. 6, that of dihydroxyacetone alone has a peak at 265 mμ. A mixture of dihydroxyacetone (0·115M) and glyoxal (0·24M) gave a spectrum similar to that of the irradiated glucose solution. Moreover, the ultraviolet spectrum of a solution of D-glyceraldehyde had no peak but, on the addition of a small amount of alkali to the solution, the spectrum became identical with that of dihydroxyacetone. This behaviour was thus similar to that of the irradiated solution of glucose on treatment with alkali (Fig. 4). In alkali 2-oxogluconic acid enolised and gave a spectrum with a peak of 275 and minimum at 250 mμ (Fig. 6).

Formation of Hydrogen Peroxide during Irradiation.—The results obtained by colorimetric estimation of hydrogen peroxide with titanium sulphate [14] are represented in Fig. 7. In the initial stages, the rate of formation of the peroxide was constant until 4×10^{17} molecules per ml. had been formed, but then fell as equilibrium was established.

When irradiation ceased, the peroxide decreased at a rate of 3×10^{13} molecules ml.$^{-1}$ min.$^{-1}$, which is comparable with the decrease (4×10^{13}) observed when glucuronic acid and hydrogen peroxide are mixed under similar conditions. After 7 days this solution did not exhibit absorption at 265 mμ.

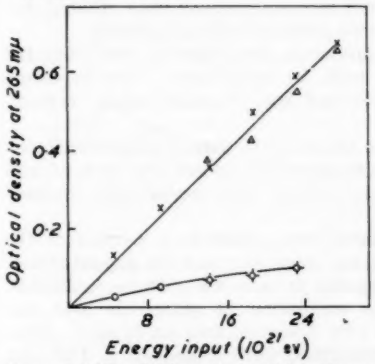
Separation of Neutral and Acidic Products.—Before the application of the isotope dilution method, attempts were made to separate the neutral and the acidic constituents by the use of ion-exchange resins. Inasmuch as Phillips and Pollard [13] observed considerable degradation

[14] Eisenberg, *Ind. Eng. Chem., Analyt. Ed.*, 1943, **15**, 327.
[11] Phillips and Pollard, *Nature*, 1953, **171**, 41.

of glucose and almost complete retention on Amberlite, and Machell [16] found difficulty in removing sugar lactones from Deacidite FF, we employed less basic exchangers. The best separations were obtained with Deacidite E and Zeo-Karb 225. By using the former charged with N-sodium hydroxide, quantitative recovery of neutral sugars was possible.

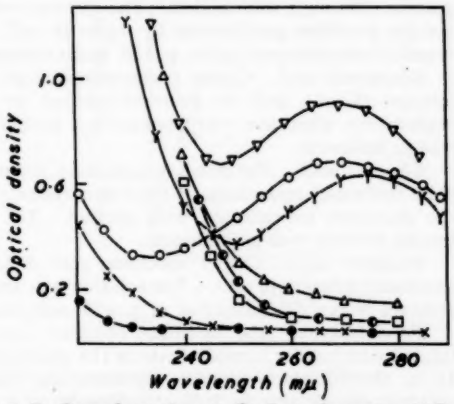
In a typical experiment, an aqueous solution (150 ml.) of glucose (7·8 millimoles) of specific activity 10·2 μc/millimole was irradiated at a dose rate of $2{\cdot}13 \times 10^{17}$ ev min.$^{-1}$ ml.$^{-1}$ in a stream of oxygen for 24 hr. The solution was passed through a column of Deacidite E which was washed with water to produce 250 ml. of eluant (neutral fraction). The acids were removed from the column with 2N-ammonia, and the free acids liberated by passage through a column of Zeo-Karb 225. The eluted solution was made up to 100 ml. (acid fraction).

FIG. 5. *Increase in ultraviolet absorption at 265 mμ with energy input during irradiation of aqueous* D-*glucose.*



Dose rate $9{\cdot}65 \times 10^{16}$ ev min.$^{-1}$ ml^{-1}. *Glucose concn.* (Δ) 5×10^{-2}M (*vac.*), (×) 5×10^{-3}M (*vac.*), (○) 5×10^{-2}M (O_2), (-◇-) 5×10^{-3}M (O_2).

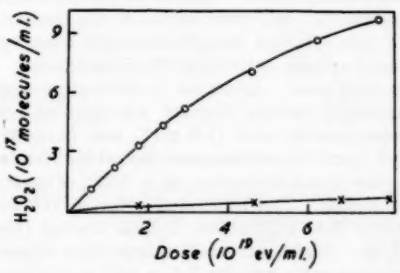
FIG. 6. *Ultraviolet absorption spectra of aqueous solutions.*



● Ca 2-*oxogluconate.* × Ca 5-*oxogluconate.* Y Ca 2-*oxogluconate in aq.* NaOH. ○ 1 : 3-*Dihydroxyacetone.* △ *Glyoxal.* ▽ *Mixture of the previous two.* □ D-*Glucuronolactone.* ◐ D-*Gluconolactone.*

FIG. 7. *Formation of hydrogen peroxide during irradiation of aqueous* D-*glucose with* ^{60}Co γ *radiation.*

Glucose concn. 5×10^{-2}M. *Dose rate* $9{\cdot}65 \times 10^{16}$ ev. min.$^{-1}$ ml.$^{-1}$. ○ O_2. × *Vacuum.*



Chromatography of the fractions gave no clear-cut separations. The radioactivity of the spots was measured, and the results are shown in Table 2, where the units refer to counts per 5 min.

TABLE 2. *Relative amounts of products.*

Product	Acidic fraction	Neutral fraction	Unseparated mixture
Glucose	342	2366	2610
Glucuronic acid (lactone + free acid)	36	230	262
Compound (R_F 0·22)	40	128	170

[16] Machell, *J.*, 1957, 3389.

Unchanged glucose and the main products in the acidic and the neutral fractions were quantitatively estimated by the isotope dilution method (Table 3*a*), and where possible the data in Table 2 were used to estimate the products in the whole irradiated mixture.

Estimation of Products by Isotope Dilution Method.—The isotope dilution method applied directly to the irradiated mixture confirmed the results obtained by paper chromatography. In a typical estimation an aqueous solution (100 ml.) of glucose (11·07 millimoles) of specific activity 2·8 μc/millimole was irradiated at a dose rate of $2{\cdot}13 \times 10^{17}$ ev min.$^{-1}$ ml.$^{-1}$ in oxygen for 46·5 hr. The isotope dilution method was applied directly to the untreated irradiated solution.

Glucose. The irradiated solution (10 ml.) was freeze-dried and any trace of water removed *in vacuo*. Carrier D-glucose (1·37 millimoles), acetic anhydride (1 ml.), and fused sodium acetate (200 mg.) were added. The mixture was kept at 100° for 2·5 hr., and the penta-*O*-acetate was then precipitated by water (5 ml.). After 9 recrystallisations from ethanol, the penta-*O*-acetylglucose had m. p. 135° and a constant specific activity 0·952 μc/millimole.

Glucuronic acid. Carrier D-glucuronolactone (0·42 millimole) was added to the irradiated solution (5 ml.), and the solution reduced to small bulk by distillation. The deposited D-glucurone after five recrystallisations melted at 175° and had constant specific activity 0·35 μc/millimole.

Gluconic acid. The irradiated solution (10 ml.) was treated with carrier D-gluconolactone (0·52 millimole) and excess of calcium carbonate. The solution was filtered after 2 days, and the gluconate precipitated with ethanol. Ten recrystallisations gave material of constant specific activity 0·44 μc/millimole.

Saccharic acid. Carrier saccharic acid (0·35 millimole) was added to a portion of the irradiated solution (5 ml.). The solution was treated in the usual way, and the deposited acid after six recrystallisations had m. p. 125° and constant specific activity $6{\cdot}8 \times 10^{-3}$ μc/millimole.

Formaldehyde. The distillate obtained during the estimation of glucuronic acid was treated with carrier formaldehyde (0·113 millimole) and 10% dimedone solution (5 ml.). After 48 hr. the dimedone complex separated and was recrystallised until it had m. p. 189° and constant specific activity 0·02 μc/millimole.

Glyoxal. The irradiated solution (10 ml.) was treated with phenylhydrazine (1·5 ml.) and glacial acetic acid (1·0 ml.). After seven recrystallisations from benzene, glyoxal bisphenylhydrazone was obtained with m. p. 170° and constant specific activity 0·066 μc/millimole.

Dihydroxyacetone. Carrier dihydroxyacetone (1·19 mmoles), acetic acid (1 ml.), and phenylhydrazine (1·2 ml.) were added to the irradiated solution (20 ml.) and the mixture was boiled for 5 min. Seven recrystallisations from benzene gave pure D-glycerosazone, m. p. 129°, constant specific activity 0·068 μc/millimole.

D-*Arabinose.* Attempts to estimate D-arabinose as the tetra-*O*-acetate were unsuccessful. Accordingly isotope dilution was applied by using the osazone. Carrier D-arabinose (1·04 mmoles), acetic acid (1·5 ml.), and phenylhydrazine were added to the irradiated solution (10 ml.), and the mixture was boiled for 15 min. The product required ten recrystallisations to give pure D-arabinosazone, m. p. 159°, of constant specific activity 0·099 μc/millimole.

D-*Xylose.* The irradiated solution (10 ml.) after freeze-drying was treated with carrier D-xylose (1·88 millimoles), sodium acetate (160 mg.), and acetic anhydride (1 ml.) and refluxed for 2 hr. Eight recrystallisations from ethanol gave tetra-*O*-acetyl-β-D-xylose, m. p. 124°, of constant specific activity $7{\cdot}6 \times 10^{-3}$ μc/millimole.

D-*Erythrose.* A glucose solution (specific activity 4·00 μc/millimole) (150 ml.) was irradiated as above and 10 ml. were treated with carrier D-erythrose (0·68 mmole) and phenylhydrazine (2 ml.) in glacial acetic acid (1·5 ml.). The solid which separated after eight recrystallisations from benzene gave D-erythrosazone, m. p. 157°, specific activity 0·024 μc/millimole.

Table 3 shows the yields of the main products at different energy inputs under fully oxygenated conditions. In some cases where it was difficult to purify the osazones to constant specific activity by recrystallisation, a preliminary separation was carried out on an alumina column.

Rate of Formation of Products.—Accurately known amounts of irradiated [^{14}C]glucose solution which had received progressively increasing doses of radiation were chromatographed and the radioactivity of the spots was measured. The rate of formation with energy input was measured for glucuronic acid (sum of the amounts of the free acid and the lactone), the substances showing the pink spot, R_F 0·22, and the yellow spot, R_F 0·48. The rate of

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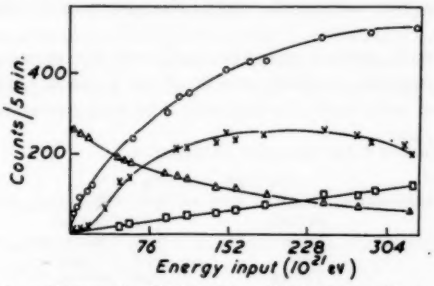
decomposition of glucose with energy input was also measured. The results are shown in Fig. 8.

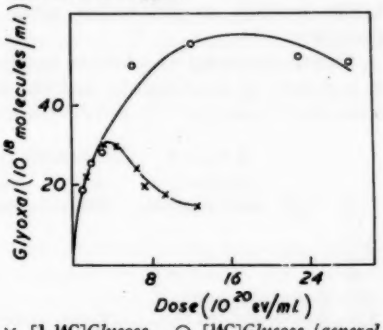
Formation of Glyoxal.—Glyoxal does not move as a discrete spot on paper chromatograms, but gives rise to extensive streaking, and in this respect resembles the behaviour of irradiated glucose solutions. To obtain the yield–dose curve for glyoxal, therefore, it was necessary to apply the more laborious isotope dilution method at each dose level. Individual experiments were carried out by using [^{14}C]glucose (generally labelled), and the glyoxal concentration measured at each dose level (Fig. 9).

FIG. 8. *Effect of energy input on rate of formation of products.*



△ D-*Glucose* (×10^{-2}). ○ D-*Glucuronic acid* + *lactone.* × *Arabinose.* □ D-*Erythrose.*

FIG. 9. *Rate of formation of glyoxal during irradiation of aqueous* D-*glucose with* ^{60}Co *γ radiation in oxygen.*



× [1-^{14}C]*Glucose.* ○ [^{14}C]*Glucose (general labelling).*

TABLE 3. *Products when aqueous solution of* D-*glucose is irradiated with gamma radiation in oxygen.*

(*a*) Initial glucose, 7·8 mmoles. Energy input, 4·6 × 10^{22} ev (*volume* 150 *ml.*).

Product:	D-Glucose	D-Erythrose	Glyoxal	Formaldehyde	D-Gluconic acid	D-Glucuronic acid	Saccharic acid
Carrier (mmole)	0·57	0·011	1·5	0·113	0·38	0·47	0·36
Sp. activity (μc per mmole) ...	4·1	3·44	0·60	0·012	2·8	0·71	0·03
Fraction	Neutral	Neutral	Neutral	Distillate	Acid	Neutral	Neutral
Yield (mmole)...	4·6	0·05 *	0·64	0·005	0·24	0·45	0·012

Corrected yield of glucose in whole irradiated solution ..... 5·2 mmoles
Corrected yield of glucuronic acid in whole irradiated solution ..... 0·50 mmole
D-Arabinose estimated from paper chromatography ..... 0·30 mmole

* Confirmed by estimation from paper chromatogram.

(*b*) Initial glucose, 5·5 mmoles. Energy input, 32·6 × 10^{22} ev (*volume* 115 *ml.*).

Product:	D-Glucose	D-Erythrose	Glyoxal	Formaldehyde	D-Gluconic acid	D-Glucuronic acid
Carrier (mmole)	1·7	0·40	1·26	0·113	1·26	0·47
Sp. activity (μc per mmole) ...	0·483	0·77	0·49	0·053	0·50	0·92
Yield (mmole) ...	1·13	0·22	0·96	0·147	0·63	1·01

D-Arabinose estimated from paper chromatogram, 0·6 mmole.

(*c*) Initial glucose, 11·07 mmoles. Energy input, 5·8 × 10^{22} ev (*volume* 100 *ml.*).

Product:	D-Glucose	D-Erythrose	Glyoxal	Formaldehyde	D-Gluconic acid	D-Glucuronic acid
Carrier (mmole)	1·37	0·68	1·13	0·113	0·52	1·04
Sp. activity (μc per mmole) ...	0·95	0·024	0·066	0·02	0·44	0·35
Yield (mmole) ...	7·05	0·09	0·85	0·05	0·44	0·60

	D-Arabinose	Saccharic acid	D-Xylose	Dihydroxyacetone
Carrier (mmole)	1·04	0·35	1·88	1·19
Sp. activity (μc per mmole)...	0·099	6·8 × 10^{-3}	7·69 × 10^{-3}	0·068
Yield (mmole)	0·45	0·016	0·06	0·31

Since glyoxal is a fragment of the glucose molecule, we have attempted to determine the part of the glucose molecule involved in its formation. The above experiment was therefore repeated with [1-^{14}C]glucose, with results shown in Fig. 9.

The rate of formation of active glyoxal is initially the same from [^{14}C]glucose and [1-^{14}C]-glucose, but after a dose of 5×10^{23} ev the rate of formation from the latter falls markedly.

Discussion

It is evident from the present work that D-glucose in aqueous solution undergoes extensive degradation under the action of ionising radiations. Solutions irradiated with 1 Mv electrons at high energy input gave chromatograms with pronounced streaking, but it was possible to distinguish spots which run identically with glucuronic acid and glucurone.

Chromatography of solutions irradiated with gamma radiation indicated the presence of a variety of constituents, and the main organic products are listed in Table 4. The behaviour of products (I) and (IV) is identical with that of glucuronic acid and glucurone,

Table 4. *Constituents in* D-*glucose solutions after irradiation.*

	Method	Irrigant	Colour	R_F	
I	Paper chromatography	Butan-1-ol–acetic acid–water	Pink	0·11	Glucuronic acid
II	,,	,,	Brown	0·18	Glucose
III	,,	,,	Pink	0·22	Arabinose
IV	,,	,,	Pink	0·34	Glucurone
V	,,	,,	Yellow	0·48	Tetrose
VI	Autoradiography	,,	—	0·75	
VII	Anilide method [13]	Water–benzene–acetone	Fluorescent (ultraviolet)	0·52	Gluconic acid

and these compounds could readily be distinguished from 2- and 5-oxogluconic acid. Since previous workers [2] have reported that glucuronic acid is not present in the irradiated solution, particular attention has been paid to the identification of this acid by paper chromatography. The presence of glucuronic acid was further confirmed by the methods of Green [12] and Abdel-Akher and Smith.[13] Moreover, oxidation of the irradiated solution with alkaline iodine gave saccharic acid, which could be formed from glucuronic acid but not from the keto-acids. Control mixtures of gluconic and glucuronic acid behaved identically with the irradiated glucose systems. In view of the variety of positive tests for glucuronic acid and the subsequent confirmation by the isotope dilution method, we conclude that this acid is formed during the irradiation.

The behaviour of fraction (III) was identical with that of arabinose. Evidence that it is neutral is furnished by the behaviour of the mixture on an ion-exchange resin (Table 2). D-Xylose might also be derived from glucose by complete removal of the primary alcohol group, but the isotope dilution method showed that its amount was very small, and that arabinose was the main pentose present. The R_F value of product V was close to that of erythrose (R_F 0·48) and dihydroxyacetone (R_F 0·52), but the colour of the *p*-anisidine complex indicated the former.

Glyoxal, erythrose, and dihydroxyacetone were detected and estimated as osazones, but the results require careful interpretation as the same osazone may be formed from different compounds and degradation of the irradiated solution may arise on treatment with phenylhydrazine. Glyoxal bisphenylhydrazone may be formed from glyoxal or glycollaldehyde. The experiments with [^{14}C]glucose and [1-^{14}C]glucose indicate that glyoxal is the predominating two-carbon fragment. Erythrosazone may be formed from D-threose, D-threulose, or D-erythrulose, but in the present connection the first two may be ruled out on configurational grounds. Since, moreover, D-erythrulose is necessarily formed by a secondary process from D-erythrose, the latter appears to be the product leading to D-erythrosazone. It is possible that the isotope dilution value corresponding to the concentration of erythrose contains a contribution from D-erythrulose. Chromatography, however, gave no indication of the presence of the latter in the irradiated

solutions and the low concentration of erythrose is more consistent with some form of secondary attack other than that involving formation of a keto-group at position 2. The possibility of degradation during the preparation of the osazones is, we consider, remote in view of the disparity between the observed amounts of glyoxal and erythrose, and we conclude that these compounds are formed by irradiation of the system. Estimation of dihydroxyacetone as D-glycerosazone does not differentiate it from D-glyceraldehyde, and the evidence, particularly that provided by the absorption spectrum of the irradiated solution, indicates that both are present.

A consistent feature of the irradiated glucose solutions is an absorption maximum at 265 mμ. This was observed for other carbohydrates by Khenokh.[17] Laurent [18] also pointed out that solutions of sugars irradiated with ultraviolet light show a similar absorption and suggested that ascorbic acid (*A*), reductone (*B*), 2-oxogluconic acid (dienol form) (*C*), and 4-deoxy-5-oxo-3 : 6-mannosaccharolactone (*D*) may be responsible. In this connection Bothner-By and Balazs [2] suggested that the absorption spectrum of glucose

TABLE 5.

	A	*B*	*C*	*D*
Max. in alkali (mμ)	265	287	275	263
Max. in acid (mμ)	245	268	230	229

solutions irradiated with *X*-rays was characteristic of ascorbic acid or the mannosaccharolactone, but our results (see Table 5) cannot be interpreted on this basis. Of the four substances mentioned, 2-oxogluconic acid is the only one admissible in the present case inasmuch as it could be formed by secondary attack on gluconic acid. We consider, however, that enolisation of 2-oxogluconic acid would not account for the absorption spectrum because the peak (265 mμ) is lower than that found for 2-oxogluconic acid and does not shift on treatment with alkali (Fig. 6). In fact, we find that when the irradiated solution is made alkaline the intensity of the peak at 265 mμ increases very markedly and the minimum of the curve moves to lower wavelength, so that the absorption is similar to that of dihydroxyacetone. The main observations may thus be interpreted on the basis of the formation of D-glyceraldehyde during irradiation and its subsequent isomerisation to dihydroxyacetone, a change which we have confirmed occurs readily in alkali. Solutions containing glyoxal and dihydroxyacetone in the proportion which they occur in the irradiated solution have practically the same absorption spectrum as the irriadiated solution (Fig. 6). We have observed that D-glucosone in alkali absorbs at 265 mμ. Isotope dilution work is now in progress to test this possibility further.

In view of our consistent identification of product (IV) as glucuronic acid by a variety of chromatographic procedures and the subsequent confirmation by the isotope dilution method, it is difficult to understand the statement by Bothner-By and Balazs [2] that "no evidence for the formation of glucuronic acid was found on any of the chromatograms." Indeed their results are not entirely consistent with this conclusion, and since the autoradiographs show the extensive streaking to which we have referred, the presence of a small amount of free acid in their solution cannot be discounted. In fact, the compound which they report as having R_F 0·32 in butan-1-ol–acetic acid–water corresponds fairly closely to the product which we have identified as D-glucuronolactone. The practice adopted by these workers of irradiating the solutions in the presence of sodium hydroxide is open to question inasmuch as some of the primary products are sensitive to alkali. Glyoxal, for example, easily forms a complex with sodium hydroxide.[19] Another complication which appears to have received no attention from these workers relates to the oxygen content of the solutions. No provision was made for replacing oxygen consumed during irradiation, and their observations cannot be related to either fully oxygenated or evacuated conditions.

[17] Khenokh, *Doklady Akad. Nauk S.S.S.R.*, 1955, **104**, 746.
[18] Laurent, *J. Amer. Chem. Soc.*, 1956, **78**, 1875.
[19] Taylor, *ibid.*, 1948, **70**, 455.

It follows that their quantitative results would be difficult to reproduce accurately. Moreover, their method of de-aerating the solution with nitrogen is not so satisfactory as the evacuation procedure, and Bourne, Stacey, and Vaughan [20] have shown that there are appreciable differences between sugar solutions irradiated in a vacuum and in nitrogen.

By the use of paper chromatography in conjunction with radioactive assay, we have determined the change in concentration of several of the products with dose (Fig. 8) for the purpose of distinguishing primary products. The rate of consumption of glucose in the early stages is constant and independent of concentration, but in the later stages the rate falls and depends on the amount of glucose present. This feature doubless arises from the competition of the products for the radicals formed during irradiation. As shown in Table 6, satisfactory correlation is found between the data obtained by the isotope dilution method and the radioactive measurements on the paper chromatograms.

TABLE 6. *Isotope dilution data and radioactive assay.*

Initial [Glucose] = 2670 counts (in 5 min.)

Energy input (10^{22} ev)	4·6	5·8	32·6
Isotope dilution			
(*a*) Initial glucose (mmole)	7·8	11·07	5·5
(*b*) Final glucose (mmole)	5·2	7·05	1·13
(*c*) Corresponding value (counts/5 min.)	1780	1700	550
Experimental value	1850	1750	600

The yield–dose curves (Fig. 8) provide valuable information as to the nature of the reactions and serve to indicate which constituents are primary products. Glucuronic acid was estimated as the sum of the free acid and lactone concentrations, and as shown in Table 7, there is close correlation between the values obtained by the chromatographic and isotope dilution methods. The yield–dose curve (Fig. 8) indicates that glucuronic acid is

TABLE 7. *Estimation of glucuronic acid.*

Energy input (10^{22} ev)	Isotope dilution	Relative value	Paper chromatogram (counts)	Relative value
4·6	0·5	1	210	1
5·8	0·6	1·2	235	1·1
32·6	1·01	2·00	525	2·16

a primary product; the rate of formation is initially constant but falls at higher doses until it becomes equal to the rate of degradation. Although, the complete yield–dose curve is not available for gluconic acid, isotope dilution data indicate that this acid is also a primary product which undergoes degradation at higher doses. The rate of formation of arabinose is low but increases at the stage where the formation of the above primary products falls off. The yield–dose curve indicates that arabinose is not a primary product and that it is degraded in the subsequent stages. The constituent with R_F 0·48 is a primary product. This appears to be erythrose, and this view is supported by the good correlation between the isotope dilution measurements and radioactive assay of the spot on a chromatogram. Experiments with [^{14}C]glucose and [1-^{14}C]glucose indicate that glyoxal is a primary product. The fact that the initial rate of formation is the same in both systems suggests that the atoms $C_{(1)}$ and $C_{(2)}$ are directly involved in the formation of the molecules. Whereas the amount of glyoxal increases in the system containing [^{14}C]glucose, the concentration reaches a maximum and then falls in the solution containing [1-^{14}C]glucose. It appears, therefore, that the glyoxal formed initially from $C_{(1)}$ and $C_{(2)}$ in the latter system is effectively diluted by the contribution from the remainder of the molecule. This evidence confirms the previous conclusion that glyoxal is the main two-carbon fragment and not glycollaldehyde, although it is possible that a certain amount of this compound may be formed at high energy inputs.

[20] Bourne, Stacey, and Vaughan, *Chem. and Ind.*, 1956, 573.

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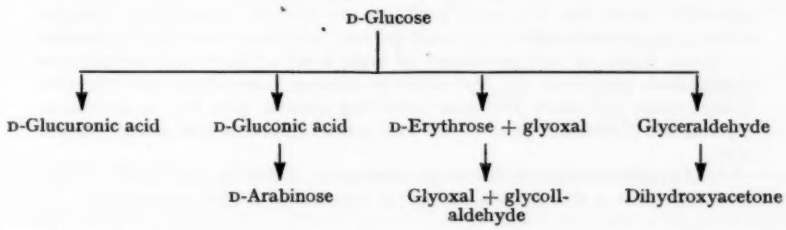
In an attempt to compare the initial G values for the products with the value corresponding to the initial rate of decomposition of glucose, we find that the yield–dose curve for the consumption of glucose is linear below $4{\cdot}6 \times 10^{22}$ ev and corresponds to G 3·5 for the removal of glucose. This was calculated from a single isotope dilution value at this energy input, but it is evident from the complete yield–dose curve (Fig. 8) that this value is in error by less than 5%. The available data for the products lead to the initial G values: glyoxal 1·8, glucuronic acid 0·9, gluconic acid 0·4. The contribution of other products must be small since the above primary products together correspond to G 3·1.

There is general concordance between the yields of acid obtained by irradiation with the electron-beam and gamma-radiations under the conditions employed in the present work. The fact that the overall acid yield is independent of the glucose concentration indicates that the radiation energy is absorbed by the water and that the chemical reactions are initiated by the free radicals formed. The process is independent of dose rate in the range under investigation, and the type of degradation appears to be essentially the same for the electron- and gamma-radiations.

The occurrence of post-irradiation reactions is shown by liberation of gas for 24—30 hr., and the gradual change in the absorption spectrum of the solution after irradiation. The concentration of hydrogen peroxide also falls after irradiation, and this may be due to interaction with glucuronic acid.[21] Another observation which has not been reported in detail here is the change in the paper-chromatographic pattern observed for freshly irradiated solutions and solutions which had been kept for some weeks. Similarly, inorganic phosphate continues to be liberated after irradiation of glucose 6-phosphate. These post-irradiation reactions will be considered in more detail later.



Degradation of D-glucose in aqueous solution by ionising radiations is complex and, while a detailed mechanism cannot be advanced at this stage, it is possible to indicate the main steps of the degradation in oxygen in accordance with the annexed scheme. The formation of D-glucuronic acid involves oxidation of the $CH_2{\cdot}OH$ group while that of D-gluconic acid entails ring scission, and the former reaction appears to be favoured on the basis of the observed yields. D-Arabinose is probably formed from gluconic acid as a result of the secondary process involving OH radicals.[22] A small amount of D-xylose doubtless arises from decarboxylation of glucuronic acid, though it does not appear to be the main secondary product arising from this acid. Similarly, the low yield of saccharic acid suggests that this is not the next stage in the oxidation of the gluconic and glucuronic acid. Another important primary degradation process is the formation of glyoxal by the initial cleavage between positions 2 and 3, and subsequently further contribution from other parts of the molecule. D-Erythrose, which is probably formed simultaneously with glyoxal is degraded extensively after its formation as indicated by its low yield. This may be a complex process, and may possibly involve the formation of further two-carbon fragments or D-glyceraldehyde. The main concentration of this product, however, arises from a primary breakdown of the hexose into two triose molecules. This is substantiated by the fact that dihydroxyacetone is formed immediately at low doses owing to the ready

[21] Everett and Sheppard, Report from Univ. Oklahoma Med. School. Dept. of Biochemistry, 1944.
[22] Bourne, Stacey, and Vaughan, *Chem. and Ind.*, 1956, 1374.

isomerisation of D-glyceraldehyde. The detailed nature of some of these processes will be investigated further.

This investigation was initiated at A.E.R.E., Harwell, during the tenure of a Harwell Fellowship. One of the authors (G. O. P.) gratefully acknowledges the award and the advice of a number of colleagues during this period. In particular, the authors thank Dr. W. Wild for initiating this research and for his constant advice and encouragement subsequently, Professor A. G. Evans for his interest and encouragement, Dr. S. T. Bowden for helpful advice and criticism, and A.E.R.E., Harwell, for financial support. Maintenance grants by A.E.R.E. Harwell (to G. J. M.) and the Department of Scientific Research (to G. L. M.) are gratefully acknowledged. We are indebted to Dr. V. C. Barry for a specimen of D-erythrosazone and Dr. D. M. W. Anderson for samples of the oxogluconic acids.

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711. *Radiation Chemistry of Carbohydrates. Part II.*[1] *Irradiation of Aqueous Solutions of Dextran with Gamma Radiation.*

By G. O. PHILLIPS and G. J. MOODY.

The degradation of dextran in aqueous solution by ^{60}Co γ-radiation is examined by measuring the amount of acid formed and the changes in optical rotation and reducing power. Chromatographic and isotope dilution methods reveal that the main products are glucose, isomaltose, isomaltotriose, gluconic acid, glucuronic acid, glyoxal, erythrose, and glyceraldehyde.

These products are considered to arise from at least two independent degradation processes: (*a*) hydrolysis to glucose, isomaltose, and isomaltotriose, while secondary reactions involving glucose give rise to erythrose, glyoxal and glyceraldehyde; (*b*) the formation of gluconic acid and glucuronic acid.

The irradiated solution shows an absorption at 265 mμ due to dihydroxyacetone, which is also formed during the irradiation of glucose solutions.

THE chemical effects of ionising radiations on aqueous dextran are interesting because it is used as a blood-plasma expander,[2] and its study follows our work on glucose.[1] Degradation of dextran is normally accomplished by acid, but yields are poor, and other methods, *e.g.*, use of heat, ultrasonic waves, and alternating electric fields, have been examined.[3] Although it is known that dextran is degraded on irradiation with fast electrons [4] or gamma radiation,[5] there is no information on the nature of the products. In the present work a straight-chain dextran, which can be synthesised by the bacterium leucenostoc, was used.[6] Dilute aqueous solutions of the polysaccharide under evacuated and fully oxygenated conditions have been irradiated with ^{60}Co γ-radiation, and the products have been identified and estimated by chromatographic, spectroscopic, and isotope dilution methods for the purpose of ascertaining the main steps of the degradation process.

RESULTS AND EXPERIMENTAL

The ^{60}Co source, irradiation vessels, dosimetric techniques, and the chromatographic, spectroscopic, and isotope dilution methods were similar to those used for glucose.[1] Reducing

[1] Part I, Phillips, Moody, and Mattok, preceding paper.
[2] (*a*) Lockwood, *Chem. and Ind.*, 1951, 46; (*b*) Joseph, *ibid.*, p. 312.
[3] Watson and Wolff, *J. Amer. Chem. Soc.*, 1955, **77**, 196.
[4] Price, Bellamy, and Lawton, *J. Phys. Chem.*, 1954, **58**, 821.
[5] Ricketts and Rowe, *Chem. and Ind.*, 1954, 189.
[6] Barker, Bourne, James, Neely, and Stacey, *J.*, 1955, 2096.

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power was measured by Somogyi's method.[7] Jeanes and Wilham's procedure [8] was used for the determination of the periodate consumed, and formic acid formed was estimated as described by Halsall, Hirst, and Jones.[9]

Identification of Products.—A solution of dextran (1·5 g.) in water (150 ml.) was irradiated in oxygen to a total energy input of $4·6 \times 10^{22}$ ev. Successive 50 ml. portions were dialysed against distilled water (500 ml.) for 24 hr. in " Visking " tubing, and the solutions were then concentrated under reduced pressure at $<35°$. The ultraviolet spectrum of the dialysate showed a maximum at 265 mμ. The dialysate was chromatographed with butan-1-ol–acetic acid–water (4 : 1 : 5), with silver nitrate and *p*-anisidine as spray reagents. This showed that the main products were isomaltotriose R_F 0·05, isomaltose R_F 0·09, glucose R_F 0·18, and erythrose R_F 0·49. Butan-1-ol–ethanol–water–ammonia (40 : 10 : 49 : 1) disclosed glucose R_F 0·08 and erythrose only, since the di- and tri-saccharides moved so slowly in this solvent. The sprayed

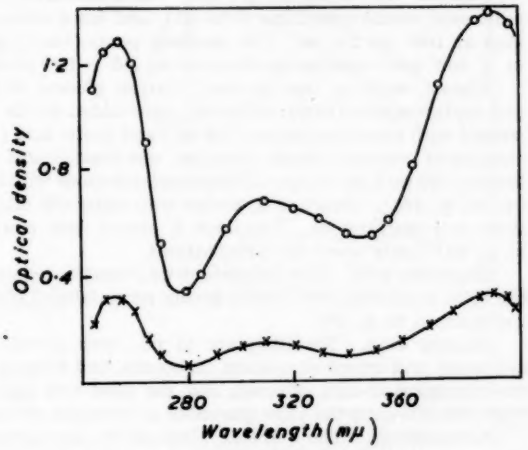

FIG. 1. *Ultraviolet absorption spectra, in methanol, of glucosazone* (○) *and a sample isolated from irradiated dextran solution* (×).

chromatograms showed the characteristic streaking found with irradiated solutions of glucose (Part I).

The solid mixture of osazones obtained by treatment of the dialysate with phenylhydrazine was separated by circular paper chromatography,[10] and the presence of glyoxal bisphenylhydrazone R_F 0·97, erythrosazone R_F 0·58, and glucosazone R_F 0·41 was established. *N*-Acetylphenylhydrazine produced from the reagents alone was also detected. The presence of erythrose, glucose, isomaltose, and isomaltotriose was confirmed by paper electrophoresis. The osazones of glyoxal, erythrose, and glucose were readily separated on a column of alumina.[10] Elution with benzene gave glyoxal bisphenylhydrazone; further treatment with ether gave erythrosazone, and ethanol–water (9 : 1) yielded glucosazone. The identity of the osazones separated in this way was confirmed by comparing the infrared spectra with those of authentic specimens. Further confirmation was furnished by the identity of the ultraviolet spectra of methanol solutions (Fig. 1) with those of authentic samples.

According to Khenokh [11] formaldehyde is one of the major products formed during the irradiation of carbohydrates since the solutions give a precipitate with phenylhydrazine. We found, however, that the distillate obtained by concentrating the irradiated solution gave a negative test for formaldehyde on treatment with dimedone or phenylhydrazine. There is evidence [12] that glyoxal bisphenylhydrazone may be formed from formaldehyde. To ascertain whether it is formed in this way, formaldehyde was subjected to the same treatment as the reaction mixture. The phenylhydrazone obtained, however, had a different m. p. (182—184°) and a different ultraviolet spectrum ($\lambda_{max.}$ 280 mμ; ε 857 in MeOH). We conclude

[7] Somogyi, *J. Biol. Chem.*, 1952, **22**, 195.
[8] Jeanes and Wilham, *J. Amer. Chem. Soc.*, 1950, **72**, 2655.
[9] Halsall, Hirst, and Jones, *J.*, 1947, 1427.
[10] Barry and Mitchell, *J.*, 1954, 4020.
[11] Khenokh, *Doklady Akad. Nauk S.S.S.R.*, 1955, **104**, 746.

that glyoxal bisphenylhydrazone is not formed from formaldehyde, and that the latter is not present as a major product. By the more sensitive test described below, it was possible to detect a small amount of formaldehyde, but its concentration was considerably lower than that of glyoxal. The presence of glyoxal in the irradiated solution was readily shown by Bamberger's test.[13] and it appears that this compound is responsible for the extensive streaking observed on the paper chromatograms.

Isotope Dilution Method.—The products were also identified and estimated by the isotope dilution method (Part I). [^{14}C]Dextran diluted with the straight-chain dextran used in the above experiments was dissolved in water (100 ml.), and the solution (0·15%; specific activity 2·7 μc/millimole of carbon) was irradiated at $2·13 \times 10^{17}$ ev min.$^{-1}$ ml.$^{-1}$ for 20·5 hr. After dialysis against two 500 ml. portions of water of the irradiated solution (89 ml.) to constant rotation the individual products were estimated in the concentrated dialysate (50 ml.).

Glucose. The dialysate (10 ml.) was freeze-dried and treated with carrier glucose (0·59 millimole), acetic anhydride (0·75 ml.), and fused sodium acetate (0·06 g.). The mixture was kept at 100° for 2·5 hr. The resulting penta-*O*-acetylglucose after six recrystallisations had m. p. 135° and constant specific activity $3·5 \times 10^{-3}$ μc/mmole.

Glucose, erythrose, and glyoxal. Carrier glucose (0·21 millimole), glyoxal (0·5 millimole), and erythrosazone (0·004 millimole) were added to the dialysate (20 ml.). The mixture was treated with phenylhydrazine (1·8 ml.) and acetic acid (1·5 ml.) at 100° for 15 min. The solid mixture of osazones which separated was fractionated on alumina. Fraction 1, eluted with benzene (95 ml.), gave glyoxal bisphenylhydrazone which after 7 recrystallisations from benzene had m. p. 169°. Fraction 2, eluted with ether (60 ml.), gave erythrosazone, m. p. 157° after three recrystallisations. Fractions 3, eluted with methanol–water (9 : 1), gave glucosazone, m. p. 201° after seven recrystallisations.

Glucuronic acid. The dialysate (5 ml.) was treated with glucuronic acid (0·41 millimole), and the solid remaining after freeze-drying recrystallised seven times from hot water to give pure D-glucurone, m. p. 175°.

Gluconic acid. The dialysate (5 ml.) was treated with carrier D-gluconolactone (0·52 millimole) and excess of calcium carbonate, and filtered after 3 days. The calcium gluconate was precipitated with ethanol, and the solid was separated. Ten successive precipitations from solution gave the pure gluconate of constant specific activity.

Formaldehyde. The distillate obtained by concentrating the irradiated solution (300 ml.) was treated with carrier formaldehyde (0·113 millimole) and 5% ethanol–dimedone (10 ml.). Four recrystallisations of the solid which separated gave the pure complex, m. p. 189°.

Dihydroxyacetone. The dialysate (10 ml.) was treated with carrier dihydroxyacetone (1·0 millimole), phenylhydrazine (1 ml.), and glacial acetic acid (0·5 ml.). The mixture was heated at 100° for 5 min. and the osazone separated. Seven recrystallisations from benzene gave pure glycerosazone, m. p. 128°, and constant specific activity. The results for the isotope dilution estimations are shown in Table 1.

TABLE 1. *Irradiation of dextran in aqueous solution* (0·15%).

Compound	Specific activity of sample (μc/mmole of carbon)	Carrier (mmole)	Amount (mg.)
Glucose			
(*a*) penta-*O*-acetate	$3·5 \times 10^{-3}$	0·59	7·9
(*b*) osazone	$1·7 \times 10^{-1}$	0·21	7·1
Erythrose	$7·9 \times 10^{-1}$	0·004	0·45
Glyoxal	$2·7 \times 10^{-3}$	0·50	0·82
Gluconic acid	$1·2 \times 10^{-3}$	0·52	5·10
Formaldehyde	$8·3 \times 10^{-3}$	0·113	0·03
Glucuronic acid	$1·3 \times 10^{-3}$	0·41	4·5
Dihydroxyacetone	$1·08 \times 10^{-3}$	1·0	2·0

Changes Produced by Irradiation.—Irradiation of straight-chain dextran in aqueous solution (1%) under evacuated conditions to a total energy input of $2·9 \times 10^{21}$ ev led to a marked fall in pH. The amount of acid formed increased linearly with dose, and the yield was slightly higher under oxygenated conditions (Fig. 2). If the acid is assumed to be monobasic, G (in oxygen) = 1·5, and G (in vacuum) = 1·1. In both cases the yield did not depend on the dose

[12] von Pechmann, *Ber.*, 1897, **30**, 2459.
[13] Bamberger, *Ber.*, 1899, **32**, 1806.

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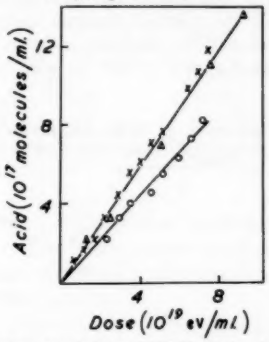
rate in the range $2{\cdot}13 \times 10^{17}$ to $9{\cdot}65 \times 10^{16}$ ev min.$^{-1}$ ml.$^{-1}$. The proportion of volatile acid was estimated in the distillate obtained by concentrating the irradiated solution. After a total dose of $6{\cdot}9 \times 10^{22}$ ev, in oxygen, the irradiated dextran solution contained 17% of the total acid in the distillate.

The optical rotation of the solution decreased steadily during irradiation, and little difference was apparent between the evacuated and the oxygenated system (Fig. 3).

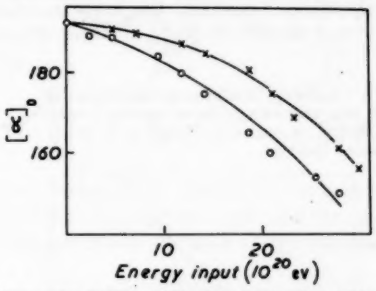
The conversion of dextran into lower saccharides would be expected to lead to an increase

FIG. 2. *Acid formation during irradiation of 0·1% aqueous dextran.*



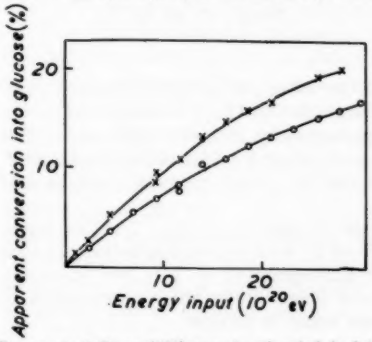
Dose rate: ×, $9{\cdot}65 \times 10^{16}$ (*in* O_2); Δ $2{\cdot}13 \times 10^{17}$ (*in* O_2); ○ $9{\cdot}65 \times 10^{16}$ (*vac.*) ev min.$^{-1}$ ml.$^{-1}$.

FIG. 3. *Change in optical rotation during irradiation of 0·1% aqueous dextran (40 ml.).*



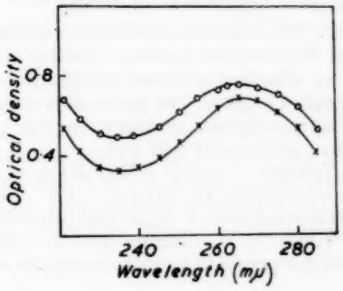
Dose rate: $9{\cdot}65 \times 10^{16}$ ev *min.*$^{-1}$ *ml.*$^{-1}$ (○) in vacuo *and* (×) *in* O_2.

FIG. 4. *Increase in reducing power during irradiation of 0·1% aqueous dextran. (40 ml.)*



Dose rate $9{\cdot}65 \times 10^{16}$ ev *min.*$^{-1}$ *ml.*$^{-1}$ (×) in vacuo *and* (○) *in* O_2.

FIG. 5. *Ultraviolet absorption spectra of* (○) *0·1% aqueous dextran after irradiation* in vacuo ($2{\cdot}78 \times 10^{21}$ ev) *and* (×) 0·19M-1 : 3-*dihydroxyacetone in* H_2O.



in the reducing power of the solution. The relation between energy input and reducing power (expressed as apparent conversion into glucose) is shown in Fig. 4. On this basis, it appears that the extent of degradation is greater under evacuated conditions.

A striking feature of the irradiation process was the change in the absorption spectrum of the solution, and the appearance of a peak at 263—266 mμ (Fig. 5). This behaviour was observed previously with glucose (Part I), and appears to be general for carbohydrates containing the glucose radical.[11] The concentration of the absorbing compound increased more rapidly with dose in the evacuated system (Fig. 6). Determinations of the absorption spectrum after irradiation had ceased revealed the occurrence of post-irradiation processes, which lead to an increase in absorption in vacuum but a decrease under oxygenated conditions. This

unusual behaviour was confirmed several times, and the results of a typical experiment are given in Table 2.

TABLE 2. *Change in absorption spectrum after irradiation.*

System	Energy input (ev)	Density at 265 mμ After irradiation	200 hr. later
Evacuated	$2{\cdot}78 \times 10^{21}$	0·75	1·02
Oxygenated	$2{\cdot}3 \times 10^{22}$	0·66	0·25
Oxygenated	$3{\cdot}0 \times 10^{21}$	0·20	0·10

Oxidation Measurements.—Extensive degradation was confirmed by oxidation of the polysaccharide fragment. To obtain comparable data for the original dextran and the final polysaccharide fragment, the lower saccharides were removed by dialysis. An oxygenated solution of dextran (0·25 g.) in water (50 ml.) was irradiated at $9{\cdot}6 \times 10^{16}$ ev min.$^{-1}$ ml.$^{-1}$ for

FIG. 6. *Increase in ultraviolet absorption at 265 mμ with energy input during irradiation* (○, in vacuo; × *in* O_2) *of* 0·1% *aqueous dextran.*

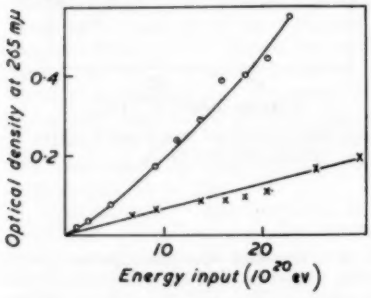
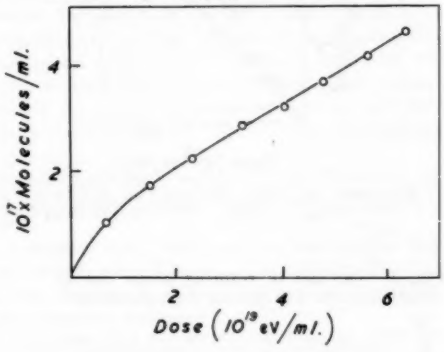


FIG. 7. *Formation of hydrogen peroxide during irradiation of* 0·19% *aqueous dextran in* O_2.



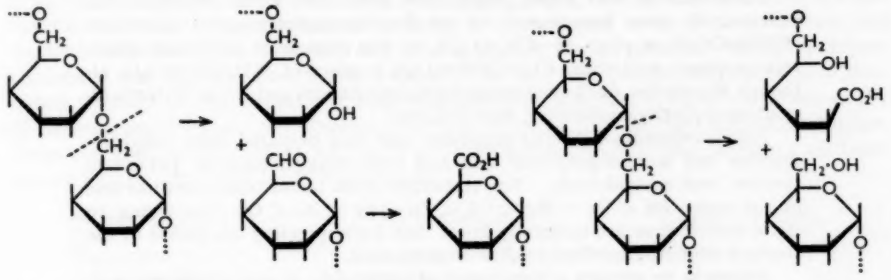
42 hr. The solution was dialysed against water (500 ml.) for 24 hr., then against running water until the rotation remained constant (0·75°). The white solid (0·11 g.) obtained on freeze-drying was shown to be homogeneous by paper chromatography and electrophoresis. This substance reduced 1·88 mols. of periodate per glucose unit forming 1·27 mols. of formic acid. Before irradiation, periodate oxidation of the original dextran gave: periodate uptake 1·96 mols.; formic acid 0·96 mol.

Hydrogen Peroxide.—Formation of hydrogen peroxide is shown in Fig. 7. The initial rate corresponds to $G(H_2O_2) = 1{\cdot}8$. As with glucose (Part I), a slow post-irradiation decrease of concentration of hydrogen peroxide was observed corresponding to 1×10^{13} molecules ml.$^{-1}$ min.$^{-1}$. No similar post-irradiation decrease was observed in the concentration of hydrogen peroxide formed during the irradiation of pure water in oxygen.

DISCUSSION

Irradiation of aqueous solutions of dextran leads to extensive degradation with formation of a polysaccharide fragment and several products of low molecular weight which can be separated from the former by dialysis. There is a steady fall in the optical rotation during irradiation, and at the same time reducing power increases, indicating the formation of lower saccharides. The evidence provided by periodate oxidation of the remaining polysaccharide fragment after irradiation is not clear. While there is no increase in periodate consumption, the amount of formic acid increases in relation to the original dextran, and it appears accordingly that a greater number of reducing end-groups are present.

From the nature of the products formed on irradiation of dextran in aqueous solution, it appears that one of the main processes is hydrolysis to glucose, isomaltose, and isomaltotriose. Estimations of glucose on the basis of isotope dilution with glucosazone and penta-*O*-acetyl-β-D-glucose are in fair agreement, and indicate that this monosaccharide is a major product: Moreover, the yield–dose curve (Fig. 4) for reducing



substances indicates that formation of glucose and other lower saccharides is a primary process. Two other major products are gluconic acid and glucuronic acid, and the over-all yield–dose curve indicates that they also are primary products, since they comprise the major acid products.

The presence of oxygen during the irradiation of aqueous solutions generally increases the yield.[14] With dextran, the reducing power of the solution indicates that there is more extensive degradation *in vacuo*, whereas slightly more acid is produced in oxygen. Bourne, Stacey, and Vaughan [15] observed similar effects in the irradiation of aqueous amylose. These anomalies, doubtless due to the occurrence of more than one primary process, reveal that oxygen plays an important rôle in determining the reaction path. Coleby [16] observed a similar behaviour with sugar lactones.

It is evident from the present results that dextran undergoes degradation by at least two independent processes involving scission at the 1—6 link of the molecule. One leads to glucose and lower saccharides, the other to gluconic and glucuronic acid. Glyoxal and erythrose, which are present in smaller amounts, are doubtless secondary products from glucose.[1] Thus random attack along the glucose chain in dextran, as indicated in the formulæ, would lead to all the main products observed. Glucose also gives rise to D-glyceraldehyde; this isomerises to 1 : 3-dihydroxyacetone, which is responsible for the strong absorption at 265 mμ. The post-irradiation processes are also similar to those found for glucose.[1] The general similarity between irradiated solutions of glucose and dextran doubtless arises from the fact that glucose-containing polysaccharides suffer hydrolysis to glucose; this is in harmony with the observations of Bourne, Stacey, and Vaughan [15] on irradiation of aqueous amylose.

The authors thank Dr. W. Wild for valuable advice, Professor A. G. Evans for his interest, and A.E.R.E., Harwell, for financial support. A maintenance grant from A.E.R.E., Harwell (to G. J. M.), is gratefully acknowledged. The authors are indebted to Professor M. Stacey, F.R.S., for providing the dextran, Professor E. J. Bourne for the [^{14}C]dextran, and Midland Silicones Ltd., Barry, for carrying out the infrared absorption measurements.

UNIVERSITY COLLEGE, CARDIFF. [*Received, April 9th*, 1958.]

[14] Stein and Weiss, *J.*, 1949, 3245; but see Dale, Davies, and Gilbert, *Biochem. J.*, 1949, **45**, 93, and Alexander and Charlesby, *Nature*, 1954, **173**, 578.
[15] Bourne, Stacey, and Vaughan, *Chem. and Ind.*, 1956, 573.
[16] Coleby, *Chem. and Ind.*, 1957, 111.

712. *Steric Hindrance in Analytical Chemistry. Part IV.* Some Sterically Hindered Complexones.*

By H. Irving, R. Shelton, and (in part) R. Evans.

Steric factors and other preparative difficulties have prevented the isolation of pure homologues of ethylenediaminetetra-acetic acid with $-CHMe\cdot CO_2H$ in place of $-CH_2\cdot CO_2H$, or homologues of ethylenediaminetetrapropionic acid with $-CH_2\cdot CHMe\cdot CO_2H$ in place of $-CH_2\cdot CH_2\cdot CO_2H$, although the nitriles, di-(2-cyanopropyl)ethylenediamine and *NNN'N'*-tetra-(2-cyanopropyl)ethylenediamine, were obtained.

Ethylenediamine-*NN'*-di-α-propionic acid was prepared from ethylenediamine and α-chloropropionic acid and from ethylenediamine, potassium cyanide, and acetaldehyde. The stabilities of its metal complexes increase in the order Ba < Ca < Mg < Cd < Zn < Co < Ni < Cu, but owing to steric factors they are uniformly lower than corresponding complexes of the stronger acid ethylenediamine-*NN'*-diacetic acid.

Attempts to prepare a homologue of anthranilic acid-*NN'*-diacetic acid gave only α-*o*-carboxyanilinopropionic acid whose metal complexes were even weaker than those of *N*-substituted glycines.

Previous papers from this laboratory have considered the effect on the stability of the corresponding proton- and metal-complexes of introducing alkyl groups into bidentate ligands such as ethylenediamine,[1] 8-hydroxyquinoline and its various aza-substituted analogues,[2] 1 : 10-phenanthroline,[3] and analogues of 2 : 2'-dipyridyl.[4,5] These studies have since been extended to ter- and multi-dentate ligands and in particular to the aminopolycarboxylic acids (complexones) of analytical importance which may formally be considered as being derived from ammonia, amines, or polyamines, by replacing two or more hydrogen atoms by carboxyalkyl residues. The effect of alkyl- or aryl-substitution on the nitrogen atoms in such complexones has been considered by Schwarzenbach and his colleagues [6,7] but hitherto no attempt has been made to examine complexones substituted (*a*) in the carboxyalkyl residues, or (*b*) in the carbon chain linking the nitrogen atoms of the parent polyamine. The first alternative forms the subject of the present paper.

Synthetic Work.—An increase in the size of a chelate ring resulting from the replacement of $-CH_2\cdot CO_2H$ by $-CH_2\cdot CH_2\cdot CO_2H$ in a complexone is known to produce less stable metal complexes.[8] We proposed to replace $-CH_2\cdot CO_2H$ in typical complexones by $-CHMe\cdot CO_2H$ and thence to study the effect of alkyl-substitution while retaining the five-membered chelate rings. The inductive effect of the methyl group would be expected to produce its customary acid-weakening effect in the ligand so that, other factors remaining equal, an increase in the stability of the corresponding metal complexes should result.[5] However, an examination of molecular models indicated that the replacement of hydrogen by methyl could introduce considerable steric hindrance to co-ordination, especially around a small cation: the net effect of the proposed substitution could not therefore be predicted.

Although ethylenediamine-*NNN'N*-tetra-acetic acid (I; R = H) and ethylenediamine-*NNN'N*-tetra-β-propionic acid can readily be prepared by condensing ethylenedi-

* Part III, *J.*, 1955, **430**.

[1] Irving and Griffiths, *J.*, 1954, 213.
[2] Irving and Rossotti, *J.*, 1954, 2910.
[3] Irving, Cabell, and Mellor, *J.*, 1953, **3417**.
[4] Irving and Williams, *Analyst*, 1952, **77**, 813.
[5] Irving and Rossotti, *Acta Chem. Scand.*, 1956, **10**, 72.
[6] Schwarzenbach, Ackermann, and Ruckstuhl, *Helv. Chim. Acta*, 1949, **32**, 1175.
[7] Schwarzenbach, Willi, and Bach, *ibid.*, 1947, **30**, 1303.
[8] Irving, Williams, Ferrett, and Williams, *J.*, 1954, 3494.

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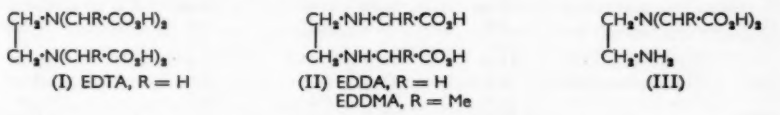
amine with chloroacetic and β-chloropropionic acid respectively in aqueous alkali, attempts to prepare ethylenediamine-*NNN'N*-tetra-α-propionic acid (I; R = Me) from ethylenediamine and α-chloropropionic acid under similar conditions gave only a dibasic acid, $C_8H_{16}O_4N_2$, shown later to be ethylenediamine-*NN'*-di-α-propionic acid (II; R = Me), even when an excess of the chloropropionic acid was employed. No evidence for the formation of any of the desired tetra-acid, $C_{14}H_{24}O_8N_2$, could be obtained from the titration curve of the mother-liquors, and when these liquors were taken to dryness and esterified with methyl alcohol with dry hydrogen chloride as catalyst, methyl α-chloropropionate was the sole identifiable product. In case the desired tetra-acid had been formed initially to any extent but had subsequently been partly decarboxylated at the pH (10) employed for the condensation, this was repeated with calcium carbonate in place of aqueous sodium hydroxide: the yield of ethylenediamine-*NN'*-di-α-propionic acid was reduced and no tetra-acid could be isolated.



(I) EDTA, R = H (II) EDDA, R = H; EDDMA, R = Me (III)

Ulrich and Ploetz [9] obtained high yields of ethylenediamine-*NNN'N'*-tetra-acetonitrile by condensing ethylenediamine with formaldehyde and hydrogen cyanide. Hydrolysis to the tetra-acid (I; R = H) presented some difficulties but a detailed study of the optimum conditions for its synthesis (using alkali cyanide in place of hydrogen cyanide [10]) permitted the yield to be raised to 96%. The condensation of ethylenediamine with acetaldehyde and potassium cyanide appeared, therefore, to be a promising route to the desired tetra-acid (I; R = Me). Unfortunately, acetaldehyde is extremely prone to condensation under alkaline conditions, but by carrying out the reaction over an extended period (76 hr.) at a low temperature (below 5°) and removing ammonia and water at intervals by vacuum-distillation (to minimise undesirable side-reactions), a fair yield of ethylenediamine-*NN'*-di-α-propionic acid was obtained. Again it appears that steric hindrance had prevented the formation of the desired tetra-acid (I; R = Me). On the assumption that this steric hindrance occurs principally when the third and the last imino-hydrogen atoms of the acid (II; R = Me) should undergo replacement by bulky groups, a more promising route appeared to be the condensation of ethylene dibromide with iminodi-α-propionitrile, $NH(CHMe{\cdot}CN)_2$, which is readily accessible,[11] although the subsequent hydrolysis might be sterically hindered or accompanied by partial decarboxylation. We have not succeeded in bringing about this condensation although a wide range of temperatures and experimental conditions have been tried, with ether, carbon tetrachloride, and toluene as media, with calcium carbonate to take up any hydrogen bromide liberated. Condensation in water under the conditions used to prepare "nitrogen mustards" [12] or *NN'*-di- or *NNN'N'*-tetra-alkylated ethylenediamines [13] were also unsuccessful.

That the acid, $C_8H_{16}O_4N_2$, should be formulated as the symmetrical ethylenediamine-*NN'*-di-α-propionic acid (II; R = Me) rather than as the unsymmetrical ethylenediamine-*NN*-di-α-propionic acid (III; R = Me) follows from the shape of its titration curve (Fig. 1) and a comparison of its proton dissociation constants with those of symmetrical and unsymmetrical ethylenediaminediacetic acids (Table 1). There is a quite remarkable agreement with the values for ethylenediamine-*NN'*-diacetic acid and ethylenediamine-*NN'*-di-β-propionic acid (despite the small difference in the temperature of measurement)

[9] Ulrich and Ploetz, U.S.P., 2,205,995/1940.
[10] Smith, Bullock, Bersworth, and Martell, *J. Org. Chem.*, 1949, 355.
[11] Dubsky, *Ber.*, 1916, **49**, 1045.
[12] Ken and Roberts, *J.*, 1950, 979.
[13] Basolo, Murmann, and Yun Ti Chen, *J. Amer. Chem. Soc.*, 1953, **75**, 1478.

and marked divergence from the values for the unsymmetrical ethylenediamine-*NN*-diacetic acid (cf. Table 1), for iminodiacetic acid, $NH(CH_2{\cdot}CO_2H)_2$ ($pK_1 = 2{\cdot}65$, $pK_2 = 9{\cdot}38$; ref. 14), for methylimino-*NN*-diacetic acid, $CH_3{\cdot}N(CH_2{\cdot}CO_2H)_2$ ($pK_1 = 2{\cdot}12$, $pK_2 = 9{\cdot}65$; ref. 15), or for hydrazine-*NN*-diacetic acid, $NH_2{\cdot}N(CH_2{\cdot}CO_2H)_2$, ($pK_1 = 2{\cdot}54$, $pK_2 = 9{\cdot}30$; ref. 16).

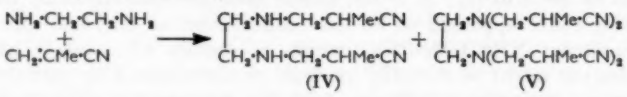
Failure to prepare the tetramethyl homologue (I; R = Me) of EDTA or to condense iminodi-β-propionitrile with dibromoethane could well be a consequence of overcrowding round the nitrogen atoms. To test this an attempt was made to prepare a homologue of

TABLE 1. *Values of stability constants at* $\mu = 0{\cdot}1$.

Ligand:	EDDA [a]	EDDMA [b]	EDDP [c]	EDDA (unsymm.) [d]
Temp.:	30°	20°	30°	20°
Ion (M)	Values of log K_{ML}			
H^+ pK_1	6·42	6·69 ± 0·02	6·87	5·58
H^+ pK_2	9·46	9·58 ± 0·02	9·60	11·05
Mg^{++}	3·9	2·8 ± 0·1	1·6	4·53
Mn^{++}	—	—	3·4	7·71
Co^{++}	11·2	10·2 ± 0·1	7·3	11·78
Ni^{++}	13·5	12·2 ± 0·1	9·3	13·73
Cu^{++}	16·2	15·2 ± 0·2	15·1	15·9
Zn^{++}	11·1	10·1 ± 0·1	7·6	11·93
Cd^{++}	8·8	8·1 ± 0·1 [e]	5·6	10·58
Ca^{++}	—	~1	—	4·63
La^{+++}	—	5·8 ± 0·1	—	—

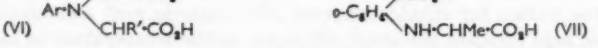
[a] Ethylenediamine-*NN'*-diacetic acid (Chabarek and Martell, *J. Amer. Chem. Soc.*, 1952, **74**, 6228). [b] Present work. [c] Ethylenediamine-*NN'*-di-β-propionic acid (Courtney, Chaberek, and Martell, *J. Amer. Chem. Soc.*, 1953, **75**, 4814). [d] Ethylenediamine-*NN*-diacetic acid (ref. 15). [e] Data given by Chabarek *et al.* (*locc. cit.*) do not take into account the formation of chloro-complexes; when allowance is made for complex-formation between cadmium ions and the 0·1M-KCl salt background, the true stability constant for this complex would be 8·8.

ethylenediamine-*NNN'N'*-tetra-β-propionic acid (which can itself be readily prepared) with methyl groups remote from the nitrogen atoms. To this end ethylenediamine was condensed with an excess of α-methylacrylonitrile, sodium ethoxide being used as catalyst. *NN'*-Di-(2-cyanopropyl)ethylenediamine (IV) and *NNN'N'*-tetra-(2-cyanopropyl)ethylenediamine (V) were obtained in yields of 30% and 11·5% respectively. Acid-hydrolysis of the dinitrile (IV) gave a small amount of an acid, which appeared to form a complex



with calcium ions: but attempts to obtain the material analytically pure failed. Alkaline hydrolysis of the dinitrile (IV) gave an uncrystallisable syrup and attempts to isolate the desired acid as its dipotassium or potassium hydrogen salt gave white crystalline materials which decomposed in a few hours. The same instability characterised products obtained by hydrolysis of the tetranitrile (V) under a variety of experimental conditions.

Schwarzenbach *et al.*[7] described a number of complexones (VI; R = R' = H) derived from aromatic amines, that from anthranilic acid forming the most stable metal complexes. Our attempts to prepare a homologue with $-CHMe{\cdot}CO_2H$ in place of $-CH_2{\cdot}CO_2H$ gave only α-*o*-carboxyanilinopropionic acid (VII), again demonstrating the difficulty of replacing



both hydrogen atoms of a primary amine by the grouping $-CHMe{\cdot}CO_2H$. When the complexone (VII) was treated with sodium chloroacetate under alkaline conditions a

[14] "Stability Constants," Part I, Chem. Soc. Special Publ., No. 6, 1957.
[15] Schwarzenbach Anderegg, Schneider, and Senn, *Helv. Chim. Acta*, 1955, **38**, 1147.
[16] Vickery, *J.*, 1954, 385.

crystalline acid resulted in 45% yield. This was doubtless the fully substituted complexone (VI; R = H, R′ = Me). It was, however, very unstable and on each successive crystallisation the melting-point range increased. Similar instability characterised *N*-methylanilinoacetic acid, for although its methyl ester, $C_6H_5{\cdot}NMe{\cdot}CH_2{\cdot}CO_2Me$, was prepared from *N*-methylaniline and methyl bromoacetate, hydrolysis gave a product which readily lost carbon dioxide and could not be obtained analytically pure. We also failed to obtain complexones pure enough for physicochemical measurements by reaction of aniline with α-bromopropionic ester, or from α- or β-naphthylamine or *o*- and *p*-arsanilic acid with chloroacetic acid or methyl bromoacetate, although crystalline products were obtained in some cases, notably when using β-naphthylamine.

Measurements of Proton– and Metal–Ligand Association Constants.—Ethylenediamine-*NN*′-di-α-propionic acid (EDDMA) (II; R = Me) and α-*o*-carboxyanilinopropionic acid (VII) were titrated potentiometrically against carbonate-free potassium hydroxide at 20·0° by means of a hydrogen electrode, a silver–silver chloride reference electrode, and a constant salt background of 0·1M-potassium chloride. Their acid dissociation constants, defined by $K_1 = [H^+][HL^-]/[H_2L]$ and $K_2 = [H^+][L^{2-}]/[HL^-]$, were calculated from the known total amount of acid taken, C_A, the hydrogen-ion concentration, $[H^+]$, and the degree of neutralisation, a, the following expression being used:

$$[H^+]^2\{aC_A + [H^+] - [OH^-]\} = K_1[H^+]\{(1-a)C_A - [H^+] + [OH^-]\} + K_1K_2\{(2-a)C_A - [H^+] + [OH^-]\} \quad . \quad (1)$$

Successive approximations were unnecessary with EDDMA since its two dissociation constants were well separated.

Similar titrations were carried out in the presence of various concentrations, C_M, of metal ions. A glass electrode and calomel reference electrode were used for titrations with copper. Calculations of stability constants, defined by $K_{ML} = [ML]/[M^{2+}][L^{2-}]$, were carried out by means of the equations:

$$C_A = [H_2L] + [HL^-] + [L^{2-}] + [ML] + 2[ML_2^{2-}] \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$C_M = [M^{2+}] + [ML] + [ML_2^{2-}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$aC_A + [H^+] - [OH^-] = [HL^-] + 2[L^{2-}] + 2[ML] + 4[ML_2^{2-}] \quad . \quad . \quad (4)$$

Under the conditions employed the 1 : 2 complex did not occur to a measurable extent and the expressions could be simplified by omitting the term $[ML_2^{2-}]$.

Results and Discussion

The titration curve of ethylenediamine-*NN*′-di-α-propionic acid (EDDMA) reproduced in Fig. 1 shows two well-separated buffer regions and corresponds to the titration of a dibasic acid with $pK_1 = 6{\cdot}69$ and $pK_2 = 9{\cdot}58$. It closely resembles those for ethylenediamine-*NN*′-diacetic acid [17] and ethylenediamine-*NN*′-di-β-propionic acid.[18] The methyl groups have produced the expected acid-weakening effect (cf. glycine with $pK_2 = 9{\cdot}78$ and β-alanine with $pK_2 = 9{\cdot}87$) and the acid strengths increase in the order EDDP < EDDMA < EDDA.

The titration curves (Fig. 1) show that the formation of complexes with the transition metals Cu^{2+}, Ni^{2+}, Co^{2+}, with Zn^{2+}, and to some extent with Cd^{2+} takes place according to the reaction:

$$H_2L + M^{2+} \longrightarrow ML + 2H^+$$

Complex formation with La^{3+} is small until the buffer region where the ion HL^- occurs. With Mg^{2+} there is only slight complex-formation even in the buffer region where L^{2-} predominates. Titration curves for EDDMA in the presence of excess Li^+, Sr^{2+}, and Ba^{2+} are indistinguishable from that of the reagent alone, showing that these ions do not form

[17] Chaberek and Martell, *J. Amer. Chem. Soc.*, 1952, **74**, 6228.
[18] Courtney, Chaberek, and Martell, *J. Amer. Chem. Soc.*, 1953, **75**, 4814.

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complexes of appreciable stability. Measurements with Ca^{2+} indicated slight complex-formation with $K < 1$.

In strongly acid solutions EDDMA could take up protons to form the cationic species $HO_2C{\cdot}CHMe{\cdot}NH{\cdot}C_2H_4{\cdot}NH_2^+{\cdot}CHMe{\cdot}CO_2H$ and possibly even

$$HO_2C{\cdot}CHMe{\cdot}NH_2^+{\cdot}C_2H_4{\cdot}NH_2^+{\cdot}CHMe{\cdot}CO_2H;$$

this can be established by titrating it with concentrated hydrochloric acid. Since copper

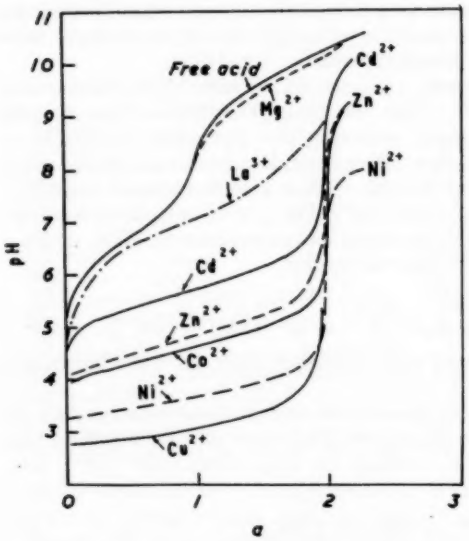


FIG. 1. *Titration curves for ethylenediamine-NN′-di-α-propionic acid and its metal complexes at 20° and* $\mu = 0{\cdot}1$M (KCl).

FIG. 2. *Correlation between the stabilities of corresponding complexes of ethylenediamine-NN′-diacetic acid* (EDDA) *and ethylenediamine-NN′-di-α-propionic acid* (EDDMA). *The broken line is that predicted theoretically for measurements all at 30°.*

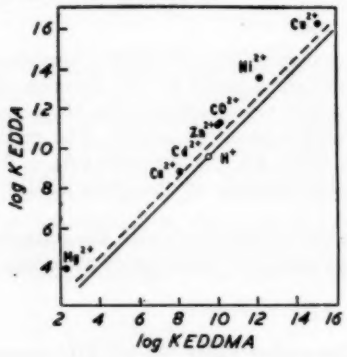
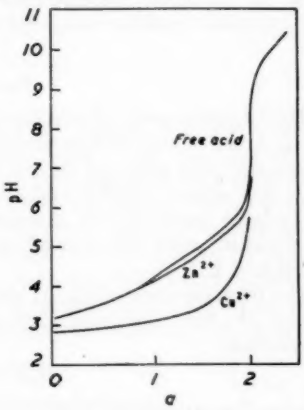


FIG. 3. *Titration curves for α-o-carboxyanilinopropionic acid and its metal complexes at 20·0° and* $\mu = 0{\cdot}1$M (KCl).



begins to form a complex with EDDMA even below pH 3, the dissociation constants of the species H_3L^+ (and possibly H_4L^{2+}) should be taken into account when calculating the stability constant of CuL. Preliminary measurements suggest that the value $K_{CuL} = 15{\cdot}2$ will not be altered significantly by such refinements.

Plots of the degree of formation, $\bar{n}$, against pL confirm the titration curves (Fig. 1) in showing that only 1 : 1 complexes are formed, even when excess of the ligand is used. EDDMA acts throughout as a quadridentate ligand.

Stability constants for the metal complexes of EDDMA are collected in Table 1 and compared with values for EDDA, EDDP, and the unsymmetrical complexone (III; R = H). The stabilities of its complexes with bivalent ions are in the order Ba < Ca < Mg < Co < Ni < Cu > Zn > Cd, thus providing another example of the Irving–Williams order [19] and the correlation of stability with the second ionisation potential.[19,20]

Since EDDMA is a weaker acid than EDDA, it would be expected to form more stable metal complexes: that the reverse is true indicates that some other factors, *e.g.*, steric effects, are operative. (The still lower stabilities of the metal complexes formed by the even weaker acid EDDP are, of course, due primarily to the increase in the size of the chelate rings.[8]) It has been shown [5] that if two very similar ligands P and Q form complexes MP and MQ with a series of metals such that the size, the number, and the geometry of the chelated rings is essentially the same, a plot of log K_{MP} against log K_{MQ} should be a straight line of unit slope and intercept ($pK_{HQ} - pK_{HP}$). For the pair of complexones ethylenediaminetetra-acetic acid and 1 : 2-diamino*cyclo*hexanetetra-acetic acid this has been shown to hold for some two dozen cations and stability constants ranging from 10^8 to 10^{24}.

Fig. 2 shows points for metal complexes of EDDA and EDDMA together with the line of unit slope (solid line) passing through the point (9·46, 9·58) and hence of the theoretical intercept. All the experimental points lie to the left of this line, showing that steric factors have weakened the metal complexes of EDDMA relatively to those of EDDA. In fact, the discrepancies become even larger than at first sight when differences in the temperatures of measurement are taken into account. Thermodynamic data for complexones and for their metal complexes are still scanty, but an increase of temperature from 20° to 30° is known to decrease pK_3 of 2-carboxyethyliminodiacetic acid, $HO_2C{\cdot}C_2H_4{\cdot}N(CH_2{\cdot}CO_2H)_2$, by 0·3 log unit, and pK_4 of EDTA (I; R = H) by about 0·5 log unit.[14] Applying the same correction to EDDMA and adopting an upper limit of $pK_2 = 9{\cdot}08$ at 30° we obtain the "theoretical" line for 30° shown (broken) in Fig. 2. Increase of temperature also reduces the strength of metal–ligand complexes to varying extents. For the change from 20° to 30° the stability of the zinc complex of 2-carboxyethyliminodiacetic acid decreases by 0·27 log unit, but that of the Mg^{2+} complex by only 0·8 log unit (ref. 14, page 57). With EDTA (ref. 14, page 76) the decreases for bivalent ions of Mg, Ca, Sr, Ba, Co, Ni, Cu, Zn, and Pb are 0·4, 0·13, 0·10, 0·9, 1·1, 1·0, 1·0, and 1·2 log units respectively, and hence all points in Fig. 2 should be displaced horizontally to the left. Unfortunately it is impossible to do more than guess the extent of the correction needed although it is likely to be very small indeed for magnesium and not more than 0·5 for the transition metals. In view of these uncertainties it is impossible to infer to what extent the steric effect is related to the ionic radius of the ion which has become the centre of the complex.

The titration curve for α-*o*-carboxyanilinopropionic acid (VII) shows a very weak inflection on the addition of one equivalent of base and a sharp rise in pH when $a = 2$, corresponding to the behaviour of a dibasic acid with $pK_1 = 3{\cdot}12$ and $pK_2 = 5{\cdot}01$, the first proton detached probably being that of the aliphatic carboxyl group. Titrations were only carried out with zinc, copper, calcium, and cadmium (Fig. 3) since it was quickly obvious that this complexone had no analytical value and that the low values of stability constants would be of little service for comparative purposes. In every case only 1 : 1 complexes were formed and the stability constants log $K_{CuL} = 6{\cdot}6 \pm 0{\cdot}2$ and log $K_{ZnL} = 2{\cdot}85 \pm 0{\cdot}1$ are well below the corresponding values for *o*-carboxyphenyliminodiacetic acid (log $K_{ZnL} = 7{\cdot}7$) or even for dimethylaminoacetic acid (log $K_{CuL} = 7{\cdot}3$).

[19] Irving and Williams, *J.*, 1953, 3192.
[20] *Idem*, *Nature*, 1948, **162**, 746.

Experimental

The titration vessel of 250 ml. capacity was constructed like a vacuum flask with double walls, and water from a thermostat at 20·0° ± 0·05° was circulated through the jacket. A tightly fitting rubber stopper carried a hydrogen electrode of the Hildebrand type, a thermometer, a mechanical stirrer, a gas-inlet tube, a silver–silver chloride electrode, and a hole for a 3 ml. microburette. The reference electrode was contained in a blackened glass tube drawn to a narrow orifice which dipped into the solution. Operation of a small rubber bulb allowed the liquid surrounding the reference electrode to be forced out and replaced by fresh titration mixture. In this way hydrogen was prevented from coming into contact with the silver electrode, and junction potentials were avoided. At the same time the arrangement provided possibilities for differential titration and gave useful indications of approaching rapid changes in the slope of titration curves.

The microburette was mounted on a rack-and-pinion device which enabled the tip to be withdrawn except when alkali was actually being delivered. This device added greatly to the precision of the measurements by preventing drifts of potential due to the slow diffusion of titrant, especially at those stages where small additions of alkali produced marked changes in hydrogen-ion concentration. The gas outlet was fitted with a soda-lime tube to prevent the back-diffusion of carbon dioxide. Hydrogen gas, freed from oxygen by means of a " De-oxo " platinum catalyst, passed through a pre-saturator (in a thermostat) containing 0·1M-potassium chloride and then through a pressure-regulator before it entered the hydrogen electrode. Potential measurements were made to 0·1 mv with a Pye " Universal " slide wire potentiometer in conjunction with a Pye " Scalamp " galvanometer. Hydrogen and silver–silver chloride electrodes were checked before and after each titration by determining the E.M.F. of the cell Ag–AgCl(s), 0·1M-HCl,H_2(Pt), and results were rejected if this differed by more than 0·2 mv from the published value.[22]

A solution of carbonate-free potassium hydroxide in potassium chloride was prepared from silver oxide and potassium chloride [23] and diluted until exactly 0·1M with respect to potassium chloride. It was stored in a vessel from which it could be transferred by hydrogen to the microburette without contact with carbon dioxide. All chemicals were of " AnalaR " grade. Doubly distilled water, tested with dithizone for freedom from traces of heavy metals, was used throughout. All metal solutions (usually 0·002M), perchloric acid (0·001M), and 0·002M-solutions of the complexones were made up in 0·1M-potassium chloride. 50 ml. of the complexone acid, x ml. of metal solution, and $(50 - x)$ ml. of 0·1M-potassium chloride were taken for each titration so that the ionic strength remained throughout at 0·1M.

Hydrogen-ion concentrations were calculated from the equation $E = E^0 + 0{\cdot}05818[H^+]$. The value of $E°$ was determined from the results of titrating a standard solution of perchloric acid (0·0009676M in 0·1M-KCl) against carbonate-free potassium hydroxide (0·09950M in 0·1M-KCl) which had been standardised potentiometrically against potassium hydrogen phthalate and recrystallised ethylenediaminetetra-acetic acid. In this and in all other neutralisations Gran's method was used to locate the exact end-point.[21] E^0 was determined daily and whenever either electrode was changed. It varied slightly with barometric pressure, the maximum variation being 2 mv.

The apparatus was tested by determining the dissociation constants of a very pure specimen of ethylenediaminetetra-acetic acid. The calculated dissociation constants, *viz.*, $pK_1 = 1{\cdot}994$, $pK_2 = 2{\cdot}674$, $pK_3 = 6{\cdot}170$, and $pK_4 = 10{\cdot}260$ agreed excellently with those reported by Schwarzenbach *et al.*,[24] *viz.*, 1·996, 2·672, 6·161, and 10·262. The results of typical titrations are tabulated.

Titrations with calcium ($C_{Ca} = 2C_A$) gave no evidence of complex-formation. The titrations with cadmium gave evidence of complex-formation after $a = 1$, but the curves were not reproducible, suggesting that the formation of hydroxy-complexes or polymeric species was also occurring to extents dependent on both pH and the time allowed between successive measurements of the E.M.F.

*Preparation of Ethylenediamine-*NN′*-di-α-propionic Acid* (II; R = Me).—(a) *From α-chloropropionic acid and ethylenediamine.* α-Chloropropionic acid (54 g., 0·5 mole) was exactly

[21] Gran, *Acta Chim. Scand.*, 1950, **4**, 559.
[22] Harned and Ehlers, *J. Amer. Chem. Soc.*, 1932, **54**, 1350.
[23] Schwarzenbach and Biedermann, *Helv. Chim. Acta*, 1948, **30**, 331.
[24] Schwarzenbach and Ackermann, *Helv. Chim. Acta.*, 1947, **30**, 1798.

(a) *Titrations with ethylenediamine-NN'-di-α-propionic acid.*

(i) Reagent alone. $C_A = 0{\cdot}00101$M.

a	pH	a	pH	a	pH	a	pH	a	pH
0	4·998	0·493	6·680	0·887	7·560	1·202	8·986	1·577	9·625
0·0591	5·620	0·542	6·766	0·946	7·860	1·242	9·080	1·680	9·750
0·0985	5·785	0·591	6·840	0·985	8·070	1·280	9·160	1·774	9·843
0·236	6·190	0·641	6·940	1·025	8·350	1·330	9·240	1·873	10·000
0·276	6·280	0·690	7·036	1·064	8·538	1·380	9·326	1·970	10·120
0·315	6·357	0·729	7·116	1·080	8·633	1·427	9·405	2·068	10·235
0·355	6·440	0·768	7·210	1·113	8·755	1·477	9·473	2·167	10·340
0·394	6·506	0·808	7·315	1·163	8·880	1·528	9·545	2·365	10·550
0·434	6·590	0·847	7·430						

(ii) Zinc. $C_A = C_{Zn} = 0{\cdot}00101$M.

a	pH	a	pH	a	pH	a	pH	a	pH
0·000	4·020	0·493	4·460	1·084	4·819	1·636	5·303	1·990	7·000
0·059	4·108	0·591	4·510	1·182	4·885	1·680	5·357	2·010	7·935
0·095	4·148	0·690	4·570	1·280	4·953	1·774	5·531	2·030	8·338
0·197	4·232	0·788	4·639	1·380	5·020	1·873	5·788	2·090	8·831
0·296	4·308	0·887	4·685	1·477	5·106	1·932	6·110	2·130	9·010
0·394	4·380	0·985	4·748	1·577	5·220	1·970	6·510	2·167	9·140

(iii) Zinc. $C_A = 2C_{Zn} = 0{\cdot}00101$M.

a	pH	a	pH	a	pH	a	pH	a	pH
0·000	4·130	0·591	4·767	1·112	6·279	1·459	7·735	1·714	9·156
0·059	4·202	0·690	4·896	1·182	6·499	1·498	8·061	1·774	9·284
0·098	4·238	0·788	5·002	1·242	6·700	1·536	8·440	1·873	9·445
0·197	4·360	0·887	5·185	1·301	6·900	1·577	8·689	1·970	9·623
0·296	4·472	0·946	5·335	1·360	7·051	1·616	8·887	2·068	9·763
0·394	4·561	1·005	5·586	1·419	7·446	1·656	8·999	2·167	9·910
0·493	4·668	1·084	6·083						

(iv) Magnesium. $C_A = C_{Mg} = 0{\cdot}00101$M.

a	pH	a	pH	a	pH	a	pH	a	pH
0·000	4·964	0·296	6·324	0·985	7·980	1·477	9·346	1·873	9·828
0·059	5·531	0·493	6·683	1·084	8·487	1·577	9·497	2·068	10·21
0·098	5·736	0·690	7·060	1·280	9·003	1·680	9·629	2·270	10·44
0·197	6·099	0·887	7·551	1·380	9·181				

A further titration in which $C_A = 31{\cdot}5C_{Mg}$ gave an identical value for $\log K_{MgL} = 10{\cdot}1 \pm 0{\cdot}1$.

(v) Cadmium. $C_A = C_{Cd} = 0{\cdot}00101$M.

a	pH	a	pH	a	pH	a	pH	a	pH
0·059	4·773	0·296	5·182	0·887	5·633	1·477	6·039	1·970	7·977
0·098	4·929	0·394	5·241	0·985	5·693	1·577	6·138	2·010	8·822
0·157	5·058	0·591	5·401	1·182	5·809	1·774	6·483	2·068	9·380
0·218	5·101	0·690	5·453	1·380	5·964	1·873	6·785	2·167	9·863

(vi) Cobalt. $C_A = 0{\cdot}00101$M, $C_{Co} = 0{\cdot}001223$M.

a	pH	a	pH	a	pH	a	pH	a	pH
0·000	3·929	0·591	4·402	1·380	4·870	1·774	5·234	1·990	5·960
0·059	3·991	0·788	4·510	1·477	4·933	1·873	5·359	2·030	8·288
0·098	4·039	0·985	4·624	1·577	5·020	1·932	5·556	2·167	9·005
0·197	4·138	1·182	4·730	1·680	5·114	1·970	5·775	2·365	9·311
0·394	4·277								

(vii) Nickel. $C_A = 0{\cdot}001005$M, $C_{Ni} = 0{\cdot}001465$M.

a	pH	a	pH	a	pH	a	pH	a	pH
0·000	3·283	0·398	3·426	1·194	3·728	1·692	4·083	1·971	4·957
0·059	3·307	0·597	3·492	1·393	3·850	1·792	4·186	1·990	5·719
0·099	3·324	0·796	3·567	1·493	3·901	1·891	4·407	2·010	6·829
0·199	3·359	0·995	3·642	1·593	3·982	1·951	4·728	2·090	7·776

(viii) Copper. $C_A = C_{Cu} = 0{\cdot}00101$M.

a	pH	a	pH	a	pH	a	pH	a	pH
0·000	2·76	0·788	2·98	1·380	3·29	1·780	3·76	1·970	5·07
0·197	2·80	0·985	3·06	1·577	3·46	1·901	4·14	2·010	6·67
0·394	2·86	1·182	3·16	1·680	3·59	1·932	4·41	2·053	7·79
0·591	2·90								

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(a) *Titrations with ethylenediamine-NN'-di-α-propionic acid (contd.).*

(ix) Lanthanum. $C_A = 0.00101$M, $C_{La} = 0.000705$M.

a	pH	*a*	pH	*a*	pH	*a*	pH	*a*	pH
0·000	4·655	0·394	6·310	0·985	6·958	1·380	7·413	1·774	8·264
0·099	5·552	0·591	6·548	1·182	7·165	1·577	7·773	1·970	8·674
0·197	5·873	0·788	6·742						

(b) *Titrations with α-o-carboxyanilinopropionic acid.*

(i) Reagent alone. $C_A = 0.001$M.

a	pH	*a*	pH	*a*	pH	*a*	pH	*a*	pH
0·000	3·229	0·697	3·778	1·154	4·488	1·692	5·389	2·010	8·561
0·0398	3·248	9·796	3·903	1·194	4·551	1·792	5·623	2·030	9·056
0·0995	3·288	0·896	4·055	1·254	4·652	1·891	5·964	2·070	9·401
0·199	3·352	0·936	4·112	1·333	4·780	1·930	6·210	2·110	9·649
0·298	3·412	0·995	4·222	1·393	4·879	1·951	6·580	2·189	9·982
0·398	3·487	1·0054	4·321	1·493	5·036	1·971	6·703	2·288	10·22
0·498	3·572	1·095	4·390	1·593	5·199	1·990	7·302	2·385	10·39
0·597	3·666								

(ii) Zinc. $C_A = C_{Zn} = 0.001$M.

a	pH	*a*	pH	*a*	pH	*a*	pH	*a*	pH
0·000	3·237	0·597	3·654	1·294	4·547	1·692	5·177	1·971	6·372
0·099	3·295	0·796	3·875	1·393	4·690	1·792	5·405	1·990	6·682
0·199	3·358	0·995	4·112	1·493	4·839	1·891	5·769	2·010	6·855
0·398	3·499	1·095	4·261	1·593	5·008	1·951	6·176	2·030	6·855

(iii) Copper. $C_A = C_{Cu} = 0.001$M.

a	pH	*a*	pH	*a*	pH	*a*	pH	*a*	pH
0·000	2·770	0·597	2·934	1·194	3·205	1·593	3·580	1·891	4·500
0·199	2·820	0·796	3·005	1·393	3·360	1·792	4·020	1·951	5·180
0·398	2·870	0·995	3·100						

neutralised with sodium hydroxide, and after the addition of ethylenediamine (6·0 g., 0·1 mole) the mixture was diluted to 165 ml. and maintained at 80—100° while an almost saturated solution of sodium hydroxide (20·0 g., 0·5 mole) was added at such a rate that the pH remained between the change-points of phenolphthalein and thymolphthalein. Towards the end of the reaction the solution was allowed to become more strongly alkaline and it was held at 80—100° for 30 min. after all the alkali had been added, then cooled and acidified to pH 2. A white solid separated which was collected, washed with distilled water (4 × 500 ml.) to remove sodium chloride, recrystallised three times from distilled water, and dried in vacuum for 3 days. *Ethylenediamine-NN'-di-α-propionic acid* forms needles, m. p. 260—265° (decomp.) [Found: C, 47·1; H, 7·8; N, 13·5%; *M* (by titration), 203·5, 305. $C_8H_{14}O_4N_2$ requires C, 47·0; H, 7·9; N, 13·7%; *M*, 204·2. Calc. for $C_{14}H_{24}O_8N_2$ (the corresponding tetra-acid): C, 48·3; H, 6·9; N, 8·0%; *M*, 348·5].

The yield was not improved by heating at 100° for 6 hr. after the addition of alkali or by conducting the condensation under the conditions used for the preparation of ethylenediamine-*NNN'N'*-tetra-β-propionic acid.

(b) *From acetaldehyde, potassium cyanide, and ethylenediamine.* By means of a dropping funnel fitted with a very fine air leak, a solution of freshly distilled acetaldehyde (14·7 g., 0·33 mole) in distilled water (200 ml.) was added continuously during 24 hr. to a stirred solution of 60% ethylenediamine (33·3 g., 0·33 mole), potassium cyanide (110 g., 1·66 mole), and sodium hydroxide (7·0 g.) diluted to 200 ml. with water and kept below 0°. Stirring was continued for some hours after addition of aldehyde, the temperature was then slowly raised to 60°, and the solution distilled under vacuum until 200 ml. of distillate had collected. The temperature was then reduced and a further 100 ml. of aqueous acetaldehyde (0·166 mole) were added during the next 12 hr. to the mixture kept at 0° and stirred as before. After removal

of 100 ml. of distillate in vacuum the sequence of operations was repeated, as shown in the following Table, until a total of 1·33 moles of acetaldehyde had been added.

Reaction time (hr.)	20	12	12	10	8	8	6
Acetaldehyde added (mole)	0·333	0·166	0·166	0·166	0·166	0·166	0·166
Temp.	−2°	0°	0°	0°	5°	5°	10°
Water removed (ml.)	200	100	100	100	100	100	200

The final red-brown solution was diluted to 1 l. and stirred while 6N-sulphuric acid was added slowly to bring the pH to 2. After a further 2 hours' stirring, the yellow precipitate was collected, washed free from potassium salts with water (4 × 500 ml.), and recrystallised 3 times from metal-free water [yield 3 g.; m. p. 262—265° (decomp.)] (Found: C, 47·3; H, 7·8; N, 13·6%; *M*, 204·8).

Preparation of α-o-*Carboxyanilinopropionic Acid* (VII).—Solutions of anthranilic acid (13·7 g., 0·1 mole) and α-chloropropionic acid (54 g., 0·45 mole) were separately neutralised with sodium carbonate, mixed, diluted to 450 ml., and heated under reflux while sodium hydroxide (8·0 g.) in water (100 ml.) was added dropwise (48 hr.), and then for a further 4 hr. After being cooled, the mixture was acidified to pH 5. α-o-*Carboxyanilinopropionic acid* separated as a yellow solid (5·3 g.) which after being decolorised (charcoal) and recrystallised three times from boiling water formed very pale yellow crystals, m. p. 178—180° (decomp.) [Found: C, 57·8; H, 5·3; N, 6·75%; *M* (by titration), 209·5. $C_{10}H_{11}O_4N$ requires C, 57·4; H, 5·3; N, 6·7%; *M*, 209·2].

Methyl N-*Methylanilinoacetate* (*With* R. Evans).—Redistilled *N*-methylaniline (21·4 g., 0·2 mole), methyl bromoacetate (46 g., 0·3 mole), anhydrous potassium carbonate (45 g.), and dry ether (150 ml.) were heated under reflux for 2 weeks. After removal of the solvent and excess of bromo-ester the main product was *methyl* N-*methylanilinoacetate*, b. p. 100—102°/1 mm. (19·5 g., 55%) (Found: C, 66·9; H, 7·4. $C_{10}H_{13}O_2N$ requires C, 67·0; H, 7·3%). The ester was obtained pure after several distillations in a vacuum but it darkened rapidly in air and was best preserved under nitrogen.

Condensation of Methacrylonitrile with Ethylenediamine.—Methacrylonitrile (200 g., 3 moles) was added dropwise (1 hr.) to freshly distilled ethylenediamine (30 g., 0·5 mole) containing as catalyst a solution of sodium (0·57 g., 0·025 mole) dissolved in the minimum amount of alcohol. After being heated under reflux for 18 hr. the mixture was left for 1 week, excess of methacrylonitrile was removed by distillation at atmospheric pressure, and the residue fractionated under reduced pressure in small portions (5 ml.). The main products were NNN′N′-*tetra*-(2-*cyanopropyl*)*ethylenediamine* (V) (19 g., 11·5%), b. p. 160—170°/1 mm. (Found: C, 65·7; H, 8·5. $C_{18}H_{28}N_6$ requires C, 65·8; H, 8·6%), and (?) NN′-*di*-(2-*cyanopropyl*)*ethylenediamine* (IV) (34·5 g., 35·5%), b. p. 103—104°/1 mm. (Found: C, 60·0; H, 9·5; N, 28·4. $C_{10}H_{18}N_4$ requires C, 61·8; H, 9·3; N, 28·8%).

Inorganic Chemistry Department,
Oxford University.

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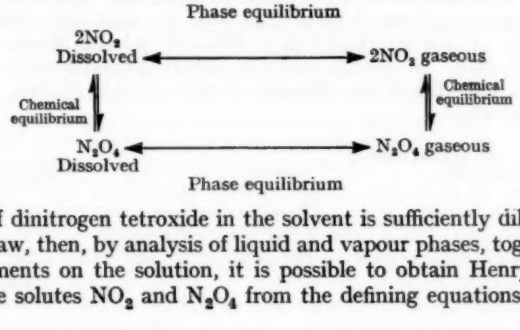
713. *Dissociation of Liquid Dinitrogen Tetroxide; Henry's Law Coefficients, Heats and Entropies of Solution, and the Thermodynamics of Homolytic Dissociation in the Pure Liquid.*

By Peter Gray and P. Rathbone.

Existing measurements of the extent of dissociation in gaseous "nitrogen dioxide" ($NO_2 + N_2O_4$ equilibrium mixture) and of saturation vapour pressure and density of the pure liquid have been correlated and combined with optical densities for both gas and liquid to calculate the extent of dissociation in the liquid. Corrections have been made for deviations from ideal-gas behaviour and thermodynamic consistency has been tested throughout.

The composition of the liquid has been determined from the freezing point (triple point, −11·2° c) to the normal boiling point (21·15°). Throughout this range, dissociation is far less in the liquid than in the gas, so the liquid can be regarded as a very dilute solution of nitrogen dioxide in dinitrogen tetroxide and, on this basis, values determined for the Henry's law coefficients of NO_2 in solvent N_2O_4 and for the (hypothetical) vapour pressure of pure liquid N_2O_4. On the same basis, standard free energy, entropy, and enthalpy changes for the dissociation $N_2O_4 \rightleftharpoons 2NO_2$ in the pure liquid can be obtained. In solvent properties (both toward gaseous NO_2 and as a medium for its own dissociation) liquid dinitrogen tetroxide is not anomalous but takes its place among other solvents, such as benzene, carbon tetrachloride, chloroform, and carbon disulphide, in which the dissociation has been examined.

Dinitrogen tetroxide dissociates reversibly in the gaseous phase, in the pure liquid, and in solution. When a solution of dinitrogen tetroxide in an inert solvent is in equilibrium with the vapour phase a number of equilibria are set up: phase equilibria between the solvent and its vapour, between dissolved and gaseous NO_2 and N_2O_4, and chemical equilibria between N_2O_4 and NO_2 in both the liquid and the gaseous phase (see diagram).



If a solution of dinitrogen tetroxide in the solvent is sufficiently dilute for the solvent to obey Raoult's law, then, by analysis of liquid and vapour phases, together with vapour-pressure measurements on the solution, it is possible to obtain Henry's law coefficients (k_1 and k_2) for the solutes NO_2 and N_2O_4 from the defining equations (symbols used are defined below):

$$\text{For } NO_2,\ k_1 \equiv \operatorname*{Lt}_{x_1 \to 0} (y_1P/x_1) \qquad \text{For } N_2O_4,\ k_2 \equiv \operatorname*{Lt}_{x_2 \to 0} (y_2P/x_2)$$

Atwood and Rollefson [1] calculated the Henry's law coefficients of NO_2 and N_2O_4 in carbon tetrachloride, and found $k_1 = 76$ atm. and $k_2 = 2{\cdot}5$ atm.

Hitherto it has been assumed that gaseous NO_2 and N_2O_4 behave ideally. However, in order to obtain accurate values for the Henry's law coefficients of NO_2 and N_2O_4, the experimental results must be corrected for gas imperfections (Appendix). In the saturated vapour, dinitrogen tetroxide is considerably dissociated; the degrees of dissociation at

[1] Atwood and Rollefson, *J. Chem. Phys.*, 1941, **9**, 506.

the freezing point (−11·2°) and at the boiling point (+21·15°) are 8·6% and 15·9% respectively. However, in the liquid phase, homolytic dissociation is very much less (0·018% at the f. p. and 0·12% at the b. p.). The electrical conductivity [2] of the liquid is minute ($1·26 \times 10^{-13}$ ohm^{-1} cm.$^{-1}$ at 0°; about that of kerosene) and thus the concentration of any ions in the liquid must be minute. Hence from the freezing to the boiling point both homolytic and heterolytic dissociation are stoicheiometrically negligible, and the liquid consists almost wholly of N_2O_4, so the liquid equilibrium mixture can be treated as a very dilute solution with N_2O_4 as solvent (and assumed to obey Raoult's law) and NO_2 as solute, and treated in terms of Henry's law:

(Partial pressure of NO_2) = (Henry's law coefficient of NO_2) × (Mole fraction of NO_2); $y_1P = k_1x_1$
(Partial pressure of N_2O_4) = (Hypothetical vapour pressure) × (Mole fraction of N_2O_4); $y_2P = P^0x_2$

From the knowledge of the Henry's law coefficient of NO_2 at different temperatures, the standard free energy of solution for each temperature, and the mean standard entropy and enthalpy of solution over the temperature range can be obtained. The combination of these results with accurate thermodynamic data [3] for gaseous equilibrium enables self-consistent thermochemistry for the dissociation in the liquid phase to be established. We now derive the Henry's law coefficient for NO_2 dissolved in N_2O_4 and the hypothetical vapour pressure of pure liquid N_2O_4 from −11·2° to +21·1°.

The calculations are based on measurements of vapour pressure [3] and of gaseous equilibrium constants (K_f),[3-8] together with optical densities [9-11] of both the gaseous and the liquid state. The composition of the vapour is found from the first two; the composition of the liquid from that of the vapour, together with the optical density of gaseous and liquid phases. Hence the Henry's law coefficient of NO_2 and hypothetical vapour pressure of N_2O_4 can be determined. Our treatment appears to be the first to assess the influence of gas imperfections, to specify standard states correctly, and to check consistency. The results differ significantly from previous ones.

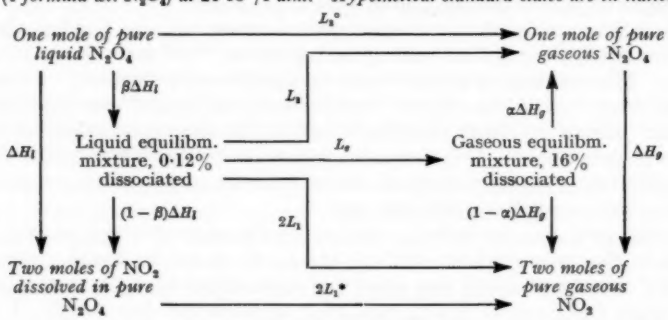
We use the following symbols: c_1 and c_2 are the concentrations of NO_2 and N_2O_4 respectively in the gaseous phase, and c_1' and c_2' those in the liquid phase (moles/l.); $\Delta G°$ and ΔG_l^* are the standard free energy of dissociation of N_2O_4 in the gaseous and the liquid phase (cal./mole of N_2O_4), and ΔG_s^* the standard free energy of solution of gaseous NO_2 in liquid N_2O_4 to form an ideal dilute solution of NO_2 in N_2O_4 of unit activity (cal./mole of N_2O_4); ΔH_g and ΔH_l are the enthalpies of dissociation (cal./mole of N_2O_4) in the gaseous and the liquid phase; K_c and K_c' are equilibrium constants (moles/l.) in terms of concentration, and K_x and K_y in terms of mole fractions, in the liquid and the gaseous phase; K_f and K_p are equilibrium constants (atm.) in the gaseous phase in terms of fugacities and partial pressures; k is the Henry's law coefficient (atm.) of NO_2 in N_2O_4; L_e is the enthalpy of vaporisation of liquid equilibrium mixture (cal./mole of N_2O_4) at 21·15°/1 atm.; L_1 is the enthalpy of vaporisation of the same mixture (cal./mole of NO_2) to give pure gaseous N_2O_4 at 21·15°/1 atm.; L_1^* is the standard enthalpy of solution of gaseous NO_2 (cal./mole of NO_2) to form an infinitely dilute solution of NO_2 in N_2O_4 at 21·15°/1 atm.; L_2 is the enthalpy of vaporisation of liquid equilibrium mixture (cal./mole of N_2O_4) to give pure gaseous N_2O_4 at 21·15°/1 atm.; $L_2°$ is the standard enthalpy of vaporisation (cal./mole of N_2O_4) of pure liquid N_2O_4 to give pure gaseous N_2O_4 at 21·15°/1 atm.; P is the vapour pressure (atm.) of the equilibrium mixture; $P°$ is the hypothetical

[2] Bradley, *Trans. Faraday Soc.*, 1956, **52**, 1255.
[3] Giauque and Kemp, *J. Chem. Phys.*, 1938, **6**, 40.
[4] Natanson and Natanson, *Ann. Physik*, (*a*) 1885, **24**, 454; (*b*) 1886, **27**, 606.
[5] Bodenstein and Boës, *Z. phys. Chem.*, 1922, **100**, 75.
[6] Wourtzel, *Compt. rend.*, 1919, **169**, 1397.
[7] Bodenstein and Katayama, *Z. phys. Chem.*, 1909, **69**, 26.
[8] Verhoek and Daniels, *J. Amer. Chem. Soc.*, 1931, **53**, 1250.
[9] Cundall, *J.*, (*a*) 1891, **59**, 1076; (*b*) 1895, **67**, 794.
[10] Steese and Whittaker, *J. Chem. Phys.*, 1956, **24**, 776; Whittaker, *ibid.*, p. 780.
[11] Hall and Blacet, *J. Chem. Phys.*, 1940, **24**, 1745.

vapour pressure of pure liquid N_2O_4; ΔS° and ΔS^* are the standard entropy of dissociation (cal./deg. per mole of N_2O_4) of N_2O_4 in the gaseous and the liquid phase; ΔS_s^* is the standard entropy of solution of gaseous NO_2 in liquid N_2O_4 (cal./deg. per mole of N_2O_4) to form an ideal dilute solution (unit activity) of NO_2 in N_2O_4; V_g and V_l are the volumes (cm.^{3}/mole) of gaseous and liquid equilibrium mixture per formula weight of N_2O_4; x_1 and x_2 are the mole fractions in the liquid, and y_1 and y_2 in the gaseous, phase for NO_2 and N_2O_4 respectively; α and β are the degrees of dissociation of N_2O_4 in the gaseous and the liquid phase; ε and ε' are the optical density per unit length (cm.$^{-1}$) in the gaseous and the liquid phase, and λ_1 and λ_2 the second virial coefficients (atm.$^{-1}$) of gaseous NO_2 and N_2O_4; ρ is the density of liquid N_2O_4 (g./cm.^{3}).

Reference States.—In the gaseous phase N_2O_4 is considerably dissociated, so the pure constituents NO_2 and N_2O_4 at unit pressure (1 atm.) are convenient reference states. However, although pure liquid N_2O_4 is a natural and convenient reference state, for liquid NO_2 a better reference is the hypothetical infinitely dilute solution in N_2O_4. The reference states employed here and their relations to one another and to experimentally realizable systems are displayed in the Scheme.

SCHEME. *Interrelations among reference states for liquid–vapour system. All magnitudes refer to* 92·016 *g.* (1 *formula wt.* N_2O_4) *at* 21·15°/1 *atm. Hypothetical standard states are in italics.*



Determination of Henry's Law Coefficient of NO_2 (k) *and the Hypothetical Vapour Pressure* (P°) *of the Pure* N_2O_4 *Species.*—The equations

$$k = y_1P/x_1 \qquad y_2P = x_2P^\circ$$

show that it is necessary to know the three quantities P, y_1, and x_1.

1. *Saturated vapour pressure P.* Giauque and Kemp [3] accurately measured the vapour pressure of the equilibrium mixture from −32·8° to +21·8°, and gave an accurate empirical equation for the vapour pressure of the equilibrium mixture as a function of temperature:

$$\log_{10}P \text{ (internat. cm. Hg)} = 8{\cdot}00436 - 1753{\cdot}000/T - 1{\cdot}1807(T/1000) + 2{\cdot}094(T/1000)^2$$

This equation was used to give the vapour pressure of entry 1 in Table 1.

2. *Composition of the vapour.* The mole fractions (y_1 and y_2) in the gaseous phase can be obtained from vapour-pressure measurements and the gaseous equilibrium constant (K_f) through the equations

$$y_1^2P/y_2 \equiv K_p = K_f = \exp(-\Delta G^\circ/\boldsymbol{R}T) \qquad y_1 + y_2 = 1$$

To obtain the concentrations (c_1 and c_2) of each of the two species from the mole fractions requires correction for gas imperfection. The following equations (see Appendix) relate c and y:

$$c_1\boldsymbol{R}T = y_1P/(1 + \lambda_1P) \qquad c_2\boldsymbol{R}T = y_2P(1 + \lambda_2P)$$

Various determinations of K_p, from which K_f can be obtained, have been made. The conditions [4-8] were very varied, so that comparison of the results is difficult. Giauque

and Kemp [3] correlated all the available experimental data and their correlation represents the best set of data for the gas-phase equilibrium. They tabulated their results as values of $\Delta[(G^\circ - H_0^\circ)/T]$, where $\Delta H_0^\circ = 12{,}875 \pm 16$ cal./mole of N_2O_4. By plotting this function against temperature we obtained its value at the desired temperature, and from this ΔG°. Hence, through K_f we obtained the mole fractions and concentrations in the gaseous phase (see entries 3 to 10 of Table 1: the equilibrium "constant" in terms of concentrations K_c for various temperatures is entry 11 and its logarithm is entry 12).

TABLE 1. *Saturation vapour pressures, equilibrium constants, and optical densities used to derive composition of liquid dinitrogen tetroxide. Entries 26 to 33 are mean values. For units see definition of symbols.*

	Temp. (°K)	261·9	263·1	273·1	283·1	293·1	294·2
1	P	0·1839	0·1973	0·3454	0·5822	0·9475	1·0000
2	$-\Delta\{(G^\circ - H_0^\circ)/T\}$	38·886	38·902	39·032	39·142	39·246	39·257
3	ΔG°	2692	2641	2215	1794	1372	1325
4	10^3K_f	5·657	6·390	16·92	41·16	94·75	103·6
5	10^3K_y	30·76	32·39	48·99	70·70	100·0	103·6
6	10^2y_1	16·07	16·48	19·82	23·29	27·02	27·42
7	10^2y_2	83·93	83·52	80·18	76·71	72·98	72·58
8	$-10^2\lambda_1$	0·707	0·698	0·624	0·560	0·505	0·499
9	10^3c_1	1·377	1·508	3·062	5·857	10·695	11·417
10	10^3c_2	7·202	7·655	12·41	19·35	29·03	30·37
11	10^4K_c	2·633	2·972	7·556	17·73	39·38	42·92
12	$\log_{10} K_c$	$\bar{4}$·4205	$\bar{4}$·4730	$\bar{4}$·8783	$\bar{3}$·2487	$\bar{3}$·5953	$\bar{3}$·6327
13	ε_{6130}	0·0174	0·0185	0·0340	0·0632	0·1095	0·1163
14	ε_{5920}	0·0278	0·0300	0·0538	0·1008	0·1743	0·1834
15	ε_{5760}	0·0184	0·0195	0·0323	0·565	0·1098	0·1176
16	ε_{6130}/c_1	12·6	12·3	11·1	10·8	10·2	10·2
17	ε_{5920}/c_1	20·2	19·9	17·6	17·2	16·3	16·1
18	ε_{5760}/c_1	13·4	12·9	10·6	9·65	10·3	10·3
19	ε'_{6130}	0·046	0·050	0·094	0·167	0·284	0·299
20	ε'_{5920}	0·077	0·083	0·148	0·264	0·440	0·464
21	ε'_{5760}	0·099	0·107	0·200	0·356	0·604	0·640
22	$10^3c_1'$ $\lambda = 6130$	4·14	4·51	8·47	15·1	25·6	26·9
23	$10^3c_1'$ $\lambda = 5920$	4·34	4·68	8·34	14·9	24·8	26·2
24	$10^3c_1'$ $\lambda = 5760$	9·17	9·91	18·5	33·0	55·9	59·3
25	ρ	1·517	1·515	1·492	1·469	1·446	1·447
26	10^4x_1	3·57	3·86	7·26	13·1	22·5	23·8
27	k	94·4	95·7	108	118	131	132
28	$\log_{10} k$	1·975	1·981	2·034	2·073	2·116	2·122
29	P°	0·1544	0·1648	0·2771	0·4472	0·6931	0·7275
30	$\log_{10} P^\circ$	$\bar{1}$·189	$\bar{1}$·217	$\bar{1}$·443	$\bar{1}$·650	$\bar{1}$·841	$\bar{1}$·862
31	10^6K_x	14·7	17·3	61·5	201	593	667
32	$10^6K_c'$	2·43	2·84	9·97	32·1	93·4	105
33	$\log_{10} K_c'$	$\bar{6}$·386	$\bar{6}$·453	$\bar{6}$·999	$\bar{5}$·507	$\bar{5}$·970	$\bar{4}$·021

3. *Composition of the liquid.* NO_2 is an odd-electron molecule and hence paramagnetic. It absorbs light over a wide range, and the colour of the gas and liquid is due to its presence. The diamagnetic dimer N_2O_4 is transparent over a wide range of wavelength. Both magnetic and optical properties have been used to investigate the equilibrium in the liquid (where pressure and density methods are inapplicable); optical methods are the more accurate.

Cundall first examined the dissociation of the pure liquid in bulk and in solution in various solvents, with a white-light colorimetric technique [9] over a considerable range of temperature. Steese and Whittaker [10] improved and extended his work. They measured the optical density of both the gaseous and the liquid phase from $-10°$ to 20° with monochromatic light of three different wavelengths for which NO_2 absorbs and N_2O_4 does not. In Table 1 Steese and Whittaker's values, at different temperatures, of the absorption coefficients (ε_λ) for the saturated vapour are entries 13 to 15; the corresponding absorption coefficients (ε'_λ) for the liquid are entries 19 to 21.

If it is assumed that the ratio of the optical densities in the liquid and the vapour phase

is equal to the ratio of concentrations then the composition of the liquid phase can be determined:

$$\frac{\text{Concentration of } NO_2 \text{ in liquid}}{\text{Optical density of liquid}} = \Big/ (\text{optical density of gas/concentration of } NO_2 \text{ in gas})$$

From the known composition of the liquid, only densities are required to obtain the mole fractions x_1 and x_2 of NO_2 and N_2O_4 in the liquid phase.

For this assumption to be *exactly* true the ratio of the absorption coefficients ($\varepsilon'_\lambda/\varepsilon_\lambda$) must be completely independent of wavelength, temperature, and total pressure. These factors are now considered in more detail.

Wavelength. When a vapour is liquefied, both the intensity of optical absorption and the positions of the absorption maxima are altered. The most satisfactory comparisons of the absorption intensities are those based on the integrated intensities or peak-heights of *corresponding* maxima in the absorption spectra of the gaseous and the liquid phase respectively. When this comparison is not possible, it is best to derive values from absorption data at as many wavelengths as possible. This method was applied here to Steese and Whittaker's optical-density data for $\lambda = 6130$ Å, 5920 Å, and 5760 Å; hence the concentration of NO_2 in the liquid, at each particular temperature, can be expressed as the mean of three values.

Temperature. The absorption maxima also move with temperature (collision broadening), and to a slightly different extent for the liquid and the gaseous phase. Therefore, for any particular wavelength, the absorption coefficient in both the liquid and the gaseous phase will vary slightly with temperature, so the quotient (absorption coefficient in gaseous phase/concentration of NO_2), *i.e.*, (ε_λ/c_1), will show a definite trend with temperature, as seen from entries 16—18 of Table 1. The observations, however, are not accurate enough for this variation to be significant. At 6130 Å and 5920 Å (ε_λ/c_1) decreases with increase in temperature, and at 5760 Å has a minimum at about 10°. Mean values of (ε_λ/c_1) were used: at 6130 Å, 11·10; 5920 Å, 17·74; 5760 Å, 10·80. (The geometric mean was chosen since this corresponds to the arithmetic mean for the entropy and enthalpy of dissociation in the liquid phase.) This treatment uses the considerably greater accuracy with which the concentration of NO_2 in the gaseous phase is known. The value of the absorption coefficient in the liquid phase also depends on temperature, but the additional errors due to this are small because, first, it is the *ratio* of the optical densities which concerns the above calculations and, secondly, the temperature range is small (−11° to +21°).

Pressure. The absorption coefficient in the liquid will be virtually unaffected by increase in pressure, owing to the very small effect of increase of pressure on a condensed phase. The absorption coefficient in the gas will vary more. However the pressure range is small and the total pressure never exceeds 1 atm. As Hall and Blacet [11] found that large pressures of nitrogen did not affect the absorption coefficient or the structure of the spectrum, pressure probably does not have any appreciable effect.

The Henry's law coefficient of NO_2 and the hypothetical vapour pressure of pure liquid N_2O_4 can now be calculated (entries 27 and 29 of Table 1).

Discussion

The extent of dissociation is very much less in the liquid than in the gas phase. At the normal boiling point (21·15°/1 atm.), when the saturated vapour is 15·9% dissociated ($K_c = 4{\cdot}29 \times 10^{-3}$ mole/l.), the liquid is only 0·12% dissociated, ($K_c' = 1{\cdot}05 \times 10^{-4}$ mole/l.). Dissociation in the liquid decreases rapidly with falling temperature; it is 0·078% at 0° (K_c' is $1{\cdot}00 \times 10^{-5}$ mole/l.), and 0·038% at the triple point (−11·2°/0·184 atm.) (K_c' is $2{\cdot}43 \times 10^{-6}$ mole/l.).

The Henry's law coefficient for NO_2 dissolved in N_2O_4 varies from 94 atm. at the freezing point to 132 atm. at the boiling point. At 25° the extrapolated value is 136 atm.

This is larger than (although of the same order of magnitude as) the value for the Henry's law coefficient of NO_2 in carbon tetrachloride at 25° (76 atm.). Carbon dioxide and sulphur dioxide have been used as models by various workers in their assessment of imperfections of gaseous NO_2. For these gases in carbon tetrachloride the Henry's law coefficients are 100 and 14 atm. respectively.

When a gas (at 1 atm. pressure) forms an ideal solution in a liquid, then its Henry's law coefficient is equal to its liquefaction pressure at the temperature of the solution. If, in carbon tetrachloride, NO_2, carbon dioxide, and sulphur dioxide deviate from ideality to about the same extent, then the hypothetical liquefaction pressure of NO_2 can be estimated roughly as about 45 atm. at 25°.

The standard free energy (ΔG_s^*), entropy (ΔS_s^*), and enthalpy (L_1^*) of solution of NO_2 in solvent N_2O_4 are approximately related to the Henry's law coefficient by the equations:

$$\Delta G_s^* = \boldsymbol{R}T \ln k$$
$$\Delta S_s^* = -\mathrm{d}\Delta G_s^*/\mathrm{d}T = \boldsymbol{R}T\,\mathrm{d}\ln k/\mathrm{d}T - R\ln k, \text{ and}$$
$$L_1^* = \Delta G_s^* + T\Delta S_s^* = \boldsymbol{R}T^2\,\mathrm{d}\ln k/\mathrm{d}T$$

"Standard" and the superscript * denote changes from the dissolved state at a particular concentration (strictly, activity) to the gaseous state *at the same concentration*. Here, this concentration is 1 mole/l.

TABLE 2. *Thermodynamics of solution of* NO_2 *in* N_2O_4.

Temperature	−11·2°	−10°	0°	10°	20°	21·15°
ΔG_s^* (cal./mole of NO_2)	738	748	819	882	948	959

L_1^* (mean) = −1560 cal./mole of NO_2; ΔS_s^* (mean) = −8·60 cal./deg. per mole of NO_2.

TABLE 3. *Thermodynamics of the dissociation of* N_2O_4 *in the gaseous and the liquid phase and in various solvents at* 20°.

Solvent	$10^3K_s'$ (moles/l.)	ΔH_1^* (cal./mole)	ΔG_1^* (cal./mole)	ΔS_1^* [cal./(deg. mole)]	$10^4K_s'V$ (moles)
$SiCl_4$	17·8	20,500	5030	52·7	20·4
CS_2	13·3	19,400	5200	48·6	8·03
CCl_4	8·05	18,800	5490	45·6	7·76
$CHCl_3$	5·53	21,200	5710	52·9	4·41
C_2H_5Br	4·79	20,500	5790	50·2	3·65
C_6H_5Br	3·70	19,400	5940	45·8	4·35
C_6H_6	2·23	22,200	6240	54·4	1·98
Pure liquid	10·47	17,820	5300	43·0	5·84
Pure gas	394	13,693	32	35·7	—

Table 2 shows the values of these thermodynamic functions. The entropy of solution (−8·6 cal. per deg. per mole of NO_2) can be related to the free volume per mole of NO_2 in solution (V_f) since

$$\Delta S_s^*/\boldsymbol{R} \simeq \ln (V_f/V_g)$$

where V_g is the molar volume of NO_2 in the gaseous phase. An estimation of V_f by this method gave a result of 13 cm.^{3}/mole of NO_2 which may be compared with the geometrical volume at the same temperature of 32 cm.^{3}/mole of NO_2.

The equation which expresses enthalpy of solution of NO_2 in N_2O_4 (L_1^*) in terms of Henry's law coefficient (k) requires corrections for gas imperfections. This leads to the equation:

$$L_1^* = -\boldsymbol{R}T^2(1 + \lambda_1 P)(\mathrm{d}\ln k/\mathrm{d}T),$$

and to a value of $L_1^* = 1560 \pm 120$ cal./mole of NO_2 at the normal boiling point ($P = 1$ atm.). The data are not precise enough to reveal any significant variation with temperature.

Similarly the enthalpy of vaporization of N_2O_4, L_2°, can be obtained from the temperature dependence of the (hypothetical) vapour pressure, P°, of pure N_2O_4 since

$L_2^\circ = (1 + \lambda_2 P)\,\boldsymbol{R}T^2\,(\mathrm{d}\ln P_0^\circ/\mathrm{d}T) = 7270 \pm 30$ cal./mole of N_2O_4 at normal b. p.

This latent heat corresponds to a Trouton's "constant" of about 24·5 cal./deg. per mole of N_2O_4, which may be contrasted with the apparent Trouton's "constant" for the equilibrium mixture (L_e/T_b) which is abnormally increased to 31 cal./deg. per mole of N_2O_4 by the dissociation of gaseous N_2O_4.

Thermodynamic data for the dissociation of N_2O_4 in the gaseous state, in various solvents, and in the pure liquid, are in Table 3. The results obtained for liquid N_2O_4 lie among those for the other liquid solvents: dissociation is least in benzene ($K_c' = 2{\cdot}23 \times 10^{-5}$ mole/l.) and is greatest in silicon tetrachloride ($K_c' = 17{\cdot}8 \times 10^{-5}$ mole/l.); in all solvents dissociation is much less than in the gas phase ($K_c = 394 \times 10^{-5}$ mole/l.).

For an ideal solution the fraction (K_x/K_y) at a given temperature should be independent of the solvent, and in the case of an ideal *dilute* solution (K_c'/K_c) should depend only on the molar volume of the solvent; the product $K_c'V$ should be constant. Table 2 shows that this condition is not satisfied. There appears to be no justification for Lewis and Randall's statement that "there is no reason to suppose that solutions (*i.e.*, of $N_2O_4 + NO_2$) in chloroform are non-ideal." In fact there is every reason to expect non-ideal behaviour in chloroform and all these solvents.

The standard free energy of dissociation in the liquid phase $\Delta G^* = -\boldsymbol{R}T \ln K_c'$ is 5330 cal./mole of N_2O_4. This is the change in free energy when *one mole of* N_2O_4 dissociates into *two moles of* NO_2 *at unit concentration.*

The standard entropy of dissociation of N_2O_4 in the liquid phase (ΔS^*) varies from 54·4 cal./(deg. mole) in benzene solution to 43·0 in the pure liquid. The value in the gaseous phase is 35·7.

The enthalpy of dissociation in the liquid (ΔH_l^*) can be found either from the temperature-dependence of K_c' or from the combination of thermal data for the gaseous phase with the heats of solution (L_1^*, L_2°) here determined. The Scheme displays the enthalpy relations, and from it may be read the relation between the enthalpies of dissociation in the liquid and the gaseous phase

$$\Delta H_l = L_2^\circ + \Delta H_g - 2L_1^*$$

Since the heat of solution of NO_2 (L_1^*) can scarcely be negative, a *maximum* value for the enthalpy of dissociation in the liquid is obtained when the heat of solution of NO_2 (L_1^*) is zero; therefore the upper limit for the enthalpy of dissociation in the liquid is 20·880 cal./mole of N_2O_4.

In fact L_1^* is 1560 cal./mole of NO_2. Previously it was thought to be only 700 cal. and the enthalpy of dissociation in the liquid 19,500 cal./mole of N_2O_4. The value of the latter now found, 17,820 cal./mole of N_2O_4, is further from the limit, and the value of L_1^* seems physically more reasonable. In other solvents the enthalpies of dissociation of N_2O_4 ranging from 18,800 cal./mole of N_2O_4 in carbon tetrachloride to 22,200 in benzene have been reported. (Their precision is not high, however, and the heat of dissociation of N_2O_4 in carbon tetrachloride does not differ significantly from its value in the pure liquid.)

Appendix

Allowance for Gas Imperfections and the Precision of Gaseous Equilibrium Data.—1. *Composition of the gaseous phase.* If f_1 and f_2 are the fugacities of NO_2 and N_2O_4 in the equilibrium mixture, then the quotient (f_1^2/f_2) is the equilibrium constant K_f where $K_f = \exp(-\Delta G^\circ/\boldsymbol{R}T)$.

If it is assumed that the fugacities in the gaseous mixture satisfy Lewis and Randall's rule and that the partial pressures of the separate constituents (y_1P and y_2P) satisfy the equations

$$y_1PV = \boldsymbol{R}T(1 + \lambda_1 P) \quad \text{and} \quad y_2PV = \boldsymbol{R}T(1 + \lambda_2 P)$$

then $$f_1 = y_1P \exp(\lambda_1 P) \quad \text{and} \quad f_2 = y_2P \exp(\lambda_2 P)$$

and $$K_p = y_1^2P/y_2 = K_f \exp[(2\lambda_1 - \lambda_2)P]$$

A value of $\lambda_1 = -0{\cdot}005$ atm.$^{-1}$ at 21·1°, identical with that for carbon dioxide, was chosen; the Berthelot equation which predicts that $\lambda \propto T^{-3}$ was used to derive λ at other temperatures than the b. p. For N_2O_4 the value of $\lambda_2 = 2\lambda_1$ was chosen originally by Bodenstein and Boës, Verhoek and Daniels, and Giauque and Kemp in order to simplify the calculations. This choice leads to $K_f = K_p$, and permits the evaluation of the mole fractions (y_1 and y_2) from the equations:

$$y_1^2P/y_2 \equiv K_p = K_f = \exp(-\Delta G^\circ/\boldsymbol{R}T)$$

Excellent consistency is achieved on this basis, and as the experimental data are not precise enough to justify a different choice, the same value $\lambda_2 = -0{\cdot}01(T/294)^3$ is used here. To obtain the concentrations of NO_2 and N_2O_4 in the gaseous phase (c_1 and c_2) from the mole-fractions of NO_2 and N_2O_4 in the gaseous phase (y_1 and y_2) and the vapour pressure (P) defining equations $c_i = y_iP/\boldsymbol{R}T(1 + \lambda_iP)$ are used ($i = 1, 2$).

2. *Derivation of K_f from P–V–T data.* When Giauque and Kemp applied their corrections to derive a best value of K_f, they had to use P–V–T data. They replaced the simple equation for the dissociation of N_2O_4, *viz.*, $(PV)_{obs.} = \boldsymbol{R}T(1 + \alpha)$ by $(PV)_{obs.} = \boldsymbol{R}T(1 + \alpha + \lambda_2P)$. If α' represents the term $(PV)_{obs.}/\boldsymbol{R}T - 1$, *i.e.*, the uncorrected degree of dissociation evaluated by neglecting gas imperfections, then their treatment leads to:

$$K_f = 4(\alpha' - \lambda_1P)^2P/[1 - (\alpha' - \lambda_2P)^2]$$

(In their paper [3] this equation for K_p appears erroneously with positive signs in the parentheses.)

3. *Consistency of results.* The value of K_f at 21·15°/1 atm. used here is 0·104 atm., which corresponds to a degree of dissociation $\alpha = 0{\cdot}159$. This value is obtained directly from Giauque and Kemp's tables, although in their text [3] they state that $K_f = 0{\cdot}106$ atm., corresponding to a degree of dissociation $\alpha = 0{\cdot}161$ is the best experimental value. The inconsistency is only apparent; combination of their value $\Delta H_0^\circ = 12{,}875 \pm 16$ cal./mole of N_2O_4 with that of $\Delta\{(G^\circ - H_0^\circ)/T\}$ at 21·15° leads to $\Delta G^\circ = 1325 \pm 16$ cal./mole of N_2O_4, *i.e.*, to $K_f = 0{\cdot}104 \pm 0{\cdot}004$ atm.

4. *Liquid–vapour equilibrium. The Clapeyron–Clausius equation for a dissociating imperfect gas.* To an excellent degree of approximation the exact form of Clapeyron–Clausius equation $dP/dT = L/T\,\Delta V$ can here be written:

$$dP/dT = L_e/TV_g$$

The equation of state of the gas is here not $PV_g = \boldsymbol{R}T$ but $PV_g = \boldsymbol{R}T(1 + \alpha + \lambda_2P)$ where α is the degree of dissociation, λ_2 the second virial coefficient of the dimer, and $\boldsymbol{R}$ refers to 1 formula weight of dimer, and the approximate form of the Clapeyron–Clausius equation becomes:

$$\boldsymbol{R}T^2(d \ln P/dT) = L_e/(1 + \alpha + \lambda_2P)$$

From Giauque and Kemp's interpolation formula the left-hand side is 8020 cal.; $(1 + \alpha + \lambda_2P)$ is 1·149 at the b. p. and hence L_e is 9210 cal./mole of N_2O_4. The calorimetric value is 9110 ± 9. The agreement here is better than that found for acetic acid liquid–vapour equilibrium.

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Department of Physical Chemistry,
University of Leeds.

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714. *Physicochemical Studies on Starches. Part XV.* The Action of β-Amylase on Glycogen as shown by Molecular-weight Distribution.*

By W. A. J. Bryce, J. M. G. Cowie, C. T. Greenwood, and I. G. Jones.

The changes in molecular-weight distribution occurring during the action of β-amylase on glycogen have been investigated by analysing the sedimentation diagrams obtained on ultracentrifugation of the original glycogen and two dextrins. The resultant distribution for the β-limit dextrin suggests that all the glycogen molecules in the sample, independently of molecular size, are hydrolysed to the same relative extent. Examination of an intermediate dextrin showed that during β-amylolysis, a mechanism involving degradation of all the polysaccharide molecules to the same extent appeared to be the most probable. The significance of these results is discussed.

Methods are available for converting sedimentation-velocity diagrams obtained on the ultracentrifugation of a polymer solution into molecular-weight distributions.[1-6] Little work of this type has been carried out on the components of starch. These studies are extremely valuable, however, as the pattern of action of any degradative agent can be followed *on a molecular basis*. As a preliminary to such studies on the starch components, we have analysed the changes in molecular-size distribution occurring during the action of β-amylase on glycogen in order to investigate the action-pattern of the enzyme and determine whether it has any degree of specificity with regard to the molecular size of the substrate. (This enzyme attacks the outer chains of glycogen and hydrolyses $45 \pm 5\%$ of the polysaccharide into maltose.) No previous work on this problem has been reported, although a similar study of phosphorylase action on glycogen has been made recently by Larner, Ray, and Crandall.[7] Glycogen has the advantage for this work that it possesses the most ideal sedimentation behaviour of all the starch-type materials; the concentration dependence of its sedimentation coefficient is small,[8] and this simplifies the calculations involved.

Our recent work [9] has shown the observed boundary gradient curve of glycogen to be very wide and dependent on the method of isolation. For an analysis of the distribution of sedimentation coefficients $g(S)$, a relatively narrow molecular fraction is preferable. This is not easily obtained from material of high molecular weight,[9] and hence a subfraction of alkali-extracted glycogen was used for these studies.

If the diffusion coefficient is negligible and the sedimentation coefficient (S) is independent of the concentration (c), the refractive-index gradient curve can be converted directly into a distribution of sedimentation coefficients $g(S)$ by the expression (cf. Bridgeman [1] and Baldwin [3]):

$$g(S) = (\mathrm{d}c/\mathrm{d}x)\omega^2 t x^3 / c_o x_o^2$$

Here, ω = angular velocity (in radians/sec.); t = time (in sec.) from the start of the sedimentation; x = distance (in cm.) of a point in the boundary from the axis of rotation;

* Part XIV, *J.*, 1958, 2629.

[1] Signer and Gross, *Helv. Chim. Acta*, 1934, **17**, 726; Bridgeman, *J. Amer. Chem. Soc.*, 1942, **64**, 2349; see also references given by Kinell and Rånby in "Advances in Colloid Science," Vol. III, Interscience Publ. Inc., New York, 1950.

[3] Baldwin and Williams, *J. Amer. Chem. Soc.*, 1950, **72**, 4325; Gosting, *ibid.*, 1952, **74**, 1548; Williams, Baldwin, Saunders, and Squire, *ibid.*, p. 1542.

[3] Baldwin, *ibid.*, 1954, **76**, 402.

[4] Williams and Saunders, *J. Phys. Chem.*, 1954, **58**, 854.

[5] Williams, Saunders, and Cicirelli, *ibid.*, p. 774.

[6] Baldwin, *ibid.*, p. 1081; *Biochem. J.*, 1957, **65**, 490.

[7] Larner, Ray, and Crandall, *J. Amer. Chem. Soc.*, 1956, **78**, 5890.

[8] Bryce, Cowie, and Greenwood, *J. Polymer Sci.*, 1957, **25**, 251.

[9] Bryce, Greenwood, and Jones, *J.*, 1958, in the press.

x_0 = distance (in cm.) of the meniscus from the axis of rotation; and c_0 = total concentration of the solution. However, the above conditions are obeyed by few polymers, and $g(S)$ has normally to be corrected for three boundary effects, (1) the spreading with time due to diffusion, (2) the anomalous apparent concentration of any individual molecular species due to heterogeneity—the Johnston–Ogston effect,[10] and (3) the narrowing due to the concentration-dependence of S. One can correct for diffusion by extrapolating an " apparent distribution " $g^*(S)$ *versus* $1/xt$ to infinite time.[2] One can correct for the other two effects either by extrapolating curves of $g^*(S)$ to infinite dilution,[4,5,11] or by correcting the curve of $g^*(S)$ at a single concentration for the dependence of S on c. The latter method [3] was adopted here. In view of the complex series of manipulations involved, the method is given in outline below.

Experimental

Glycogen Sample.—Glycogen was isolated from rabbit livers by extraction with hot 30% aqueous sodium hydroxide, and was purified and characterised as described elsewhere.[9] Sedimentation measurements showed that the sample was polydisperse, containing, in addition to the main component, both small and very large material (cf. ref. 9). A subfraction was obtained as follows: a 1% solution of glycogen in 0·1M-sodium chloride was centrifuged at 20,000 r.p.m. for 15 min. (Spinco ultracentrifuge) to remove very large material as gel. Cold ethanol was then slowly added to the supernatant liquid at 0°, to give a faint yet stable precipitate (approx. 30% by volume of alcohol was required). The precipitated glycogen was then removed by centrifugation at 1500 r.p.m. for 20 min. at 0°; under these conditions, the component of low molecular weight remained in solution.

Enzyme Preparation and Digest Conditions (with W. Banks).—β-Amylase was isolated from soya-beans as described by Peat, Pirt, and Whelan.[12] It contained only an insignificant trace of maltase, and no Z-enzyme as shown by experiments on potato amylose fractions.[13] α-Amylase was also absent as shown by the molecular size of the β-limit dextrin of both amylose [14] and the glycogen (see below). The activity of the enzyme in Hobson, Whelan, and Peat's units [15] was *ca.* 20,000 units/ml.

Glycogen (1 mg./ml.) was incubated with β-amylase in the presence of 0·2M-acetate buffer of pH 4·6 at 35°. Although conversion was complete within about 2 hr., the digest was left for 24 hr. before the enzyme was deactivated by heating it on a boiling-water bath for a few moments, and the glycogen-product (Found: 41% conversion into maltose) precipitated from solution with ethanol. After centrifugation, the residual β-limit dextrin was washed with alcohol and dried with ether. A polymer-product at an intermediate stage of β-amylolysis was isolated similarly (Found: 13·2% conversion into maltose).

Concentrations of glycogen were determined by hydrolysis to glucose. The latter and the amount of maltose liberated on β-amylolysis were determined by alkaline ferricyanide.[16]

Physical Measurements.—Sedimentation measurements were made as described earlier.[9,17] The time representing the effective start of the sedimentation was obtained from the point where the curve of $\log_{10} X$ against t cut the time-axis at the value of $\log_{10} X$ for the meniscus.[17] The glycogen samples were dissolved in 0·1M-sodium chloride. Sedimentation runs for distribution analysis were carried out at 20,000 r.p.m., and a series of five photographs were taken at 6 min. intervals after the boundary had completely left the meniscus (the latter requiring about 10 min.). The concentration of glycogen was approx. 8 g./l. for these measurements.

Optical System of the Ultracentrifuge and the Measurement of the Photographic Plates.—The Spinco ultracentrifuge is equipped with a Philpot–Svensson [18] optical system, which gives the refractive index gradient curve directly. However, measurements of the height and area of the

[10] Johnston and Ogston, *Trans. Faraday Soc.*, 1946, **42**, 789.
[11] Gralén and Lagermalm, *J. Phys. Chem.*, 1952, **56**, 514.
[12] Peat, Pirt, and Whelan, *J.*, 1952, 705, 714.
[13] Cowie and Greenwood, *J.*, 1957, 4640.
[14] Cowie, Fleming, Greenwood, and Manners, *J.*, 1958, 697.
[15] Hobson, Whelan, and Peat, *J.*, 1950, 3566.
[16] Lampitt, Fuller, and Coton, *J. Sci. Food Agric.*, 1955, **6**, 656.
[17] Greenwood and Das Gupta, *J.*, 1958, 707.
[18] Philpot, *Nature*, 1938, **141**, 283; Svensson, *Kolloid Z.*, 1939, **87**, 181.

peak can be complicated by Fresnel fringes.[19] For this work, we have found an inclined bar to be more satisfactory than a wire.

When an appropriate base line has been fitted, the height (dn/dx) of at least 20 equi-spaced lamellæ at distances x_1, x_2, etc., throughout the refractive-index gradient curve has to be measured. These heights, when corrected for the angle of the inclined bar and the magnification factor of the optical system, give dn/dx values which are related to the total concentration (c) by the expression:

$$c = [\int (x/x_0)^2 \,.\, dn/dx \,.\, dx]/\Delta n$$

where x, x_0 have the values given above and Δn = specific refractive-index increment of the solute. (Trapezoidal integration is sufficiently accurate for this type of work.)

Our initial measurements were made directly from the photographic plates by using a two-dimensional travelling microscope (reading to 0·001 cm.) after the "vertical" traverse had been carefully aligned parallel to the meniscus. Heights of the two edges of the Schlieren pattern were measured. It was found most convenient to record these values and subsequent calculations directly on to a Remington–Rand printing calculator. Later measurements were made easier by printing an enlargement (9 ×) and tracing this on graph paper, corrections then being made for the additional magnification factor.

In both instances, base lines were fitted from the average of the two areas (A) under the peak and a knowledge of the concentration (c) of the solution, since

$$c = (A \tan \theta/m_1 m_2 H_1 H_2 \Delta n)(x/x_0)^2$$

where θ = angle of the inclined bar in the optical system; m_1, m_2 = magnification of the cylindrical and camera lenses; H_1 = distance between the nodal point of the condensing lens and the inclined bar; H_2 = thickness of fluid column; Δn, x, x_0 are as defined above. The calculated and the actual concentrations agreed within experimental error.

Method of Determining the Molecular-weight Distribution.—(a) *The apparent distribution of sedimentation coefficients* $g^*(S)$. This function can be derived from the relations [20] $c = c_0(x_0/x)^2$ and $S = (1/\omega^2 t) \ln (x/x_0)$. It follows that $dc = dc_0(x_0/x)^2$ and $dS = (1/\omega^2 xt)dx$, and the combination of these equations gives $dc_0/dS = (dc/dx)(x/x_0)^2 \,.\, \omega^2 xt$. The curve of dc_0/dS *versus* S is not a conventional distribution since the area under it is not unity but c_0. Normalisation of the function therefore gives the apparent distribution of sedimentation coefficients $g^*(S)$ as:

$$g^*(S) = (dc_0/dS)c_0^{-1} = dc/dx \,.\, (x/x_0)^2 \,.\, \omega^2 xtc_0^{-1}$$

This function was calculated for each sedimentation diagram for about 20 incremental values of x (*i.e.*, x_1 etc.) by taking the corresponding values of $(dn/dx)_{x_1}$ for $(dc/dx)_{x_1}$ and $\Delta x \,.\, \sum_{x=0}^{x=\infty} (dn/dx)$ for c_0; the proportionality factors disappear in the quotient $(dc/dx)/c_0$. Conversion of the values of x_i into the corresponding values of sedimentation constant S_i[by $S_i = (1/\omega^2 t) \ln (x_i/x_0)$ after correction for viscosity and temperature] then enabled the graph of $g^*(S)$ *versus* S to be plotted for the different times of sedimentation.

(b) *Elimination of the diffusion effect.* From the graphs of $g^*(S)$ *versus* S, values of $g^*(S)$ for discrete values of $10^{13}S_i$ (*i.e.*, 10, 20, 30, etc.) were taken and plotted as $g^*(S_i)$ *versus* $1/x_i t$. A graphical extrapolation was then made to $1/x_i t = 0$ to yield values of the apparent distribution corrected for diffusion effects [$g'(S)$]. In agreement with Larner, Ray, and Crandall's results,[7] the data were best represented by straight lines, and all extrapolations were made on this basis. Our results were similar to those shown in Fig. 1 of ref. 7. The graph of $g'(S)$ *versus* S was thus obtained.

(c) *Transformation of* $g'(S)$ *into* dc/dx. Before corrections can be applied for the Johnston–Ogston effect,[10] the function $g'(S)$ *versus* S has to be transformed into dc/dx *versus* x. The distribution equation can be re-written in this instance as:

$$dc/dx = g'(S) \,.\, x_0^2 c_0/x^2 \omega^2 t$$

where t is now chosen as the average time, *i.e.*, the time in the middle of the run.[7] Values of $(dc/dx)_{x_1}$ were therefore calculated from corresponding values of $g'(S)$. When values of S_i

[19] Cf. Kegeles and Gutler, *J. Amer. Chem. Soc.*, 1951, **73**, 3770.
[20] Cf. Svedburg and Pedersen, "The Ultracentrifuge," Oxford Univ. Press, 1940.

were converted into x_i by the expression $x_i = x_o \exp(S_i\omega^2 t)$, the graph of dc/dx *versus* x was obtained.

(d) *Correction for heterogeneity.* In order to correct for heterogeneity, the distribution curve dc/dx *versus* x is divided into a number of equi-spaced lamellæ, and these are regarded as different components. Every molecular species i present in a given plane x_j changes in concentration at that plane, if its sedimentation coefficient S_i varies with the total concentration c_1. Baldwin [3] has shown that the change in concentration of the species (Δc_i) is related to the change in its sedimentation coefficient (ΔS_i) in terms of a parameter ($r/\omega^2 x$), where

$$r/\omega^2 x = \ln (x_j/x_o)/\omega^2 t = S_i + c_i(\Delta S_i/\Delta c_i)$$

whence

$$\Delta c_i = c_i \Delta S_i/\{[\ln (x_j/x_o)/\omega^2 t] - S_i\}$$

To carry out these calculations, about 20 values of dc/dx at a fixed increment, Δx, were tabulated against x, and the parameter $\ln (x/x_o)/\omega^2 t$ was calculated. The change in concentration of each of the components in each successive plane was then calculated in a stepwise manner by Baldwin's method.[3]

For the first lamella (x_1), only component 1 is present and therefore its concentration $c_1 = \Delta x \,.\, (dc/dx)_{x_1}$.

For the second lamella (x_2), the total concentration is $\Delta x \sum_{x=0}^{x=x_2} (dc/dx)$, which is an increase of $\Delta x(dc/dx)_x$. If $S = S_o(1 - kc)$ (see p. 3562), the sedimentation coefficient of component 1 in this lamella $(S_1)_{x_2}$ therefore decreases by an amount $(\Delta S_1)_{x_2}$ given by $-kS_{01}\Delta x(dc/dx)_{x_2}$ where $S_{01} = S_1/(1 - kc_1)$. From Baldwin's work,[3] the corresponding change in concentration $(\Delta c_1)_{x_2}$ is thus equal to:

$$(\Delta c_1)_{x_2} = c_1 \,.\, (\Delta S_1)_{x_2}/\{[\ln (x_2/x_o)\omega^2 t] - (S_1)_{x_2}\}$$

The true concentration of component 2 (c_{02}) is thus greater than $\Delta x(dc/dx)_{x_2}$ by $-(\Delta c_1)_{x_2}$.

This calculation is repeated for all the components (i) in each lamella until the corrected concentrations (c_{oi}) of each are known. Then since $c_{oi} = \Delta x(dc/dx)_{xi}$, it follows that $(dc/dx) = c_{oi}/\Delta x$. Hence values of the corrected distribution function $g(S)$ were calculated from $g(S) = (c_{oi}/\Delta x) \,.\, (x/x_o)^2 \,.\, (\omega^2 xt/c_o)$, and the graph of $g(S)$ *versus* S obtained.

(c) *Correction for the concentration dependence of S; the extrapolation of g(S) to infinite dilution.* The distribution of sedimentation coefficients at infinite dilution $g(S_o)$ is derived from $g(S) \times (dS/dS_o)$, since $g(S_o) = c_o^{-1} \,.\, (dc_o/dS_o) = c_o^{-1} \,.\, (dc/dS) \,.\, (dS/dS_o)$. Here dS/dS_o was obtained from tabular differentiation of S_{oi} and S_i values, S_{oi} being calculated from $S_i = S_{oi}(1 - kc_i)$ where $c_i = \Delta x \sum_{x=0}^{x=x_i} (dc/dx)$, as above. Values of $g(S_o)$ when plotted against the corresponding values of S_o gave the true sedimentation coefficient distribution curve.

(f) *Calculation of the molecular-weight distribution curve.* Since the distribution of molecular weight $g(M)$ is given by:

$$g(M) = c_o^{-1}(dc_o/dM) = c_o^{-1}(dc_o/dS_o)(dS_o/dM)$$

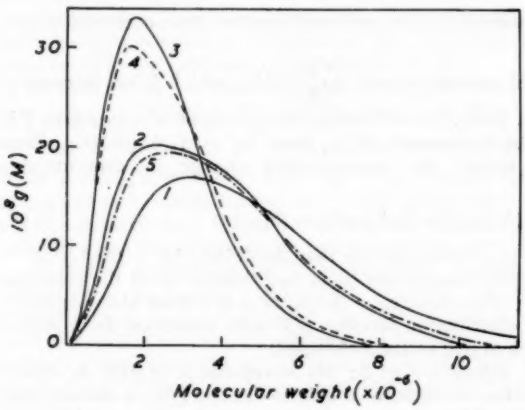
values can be calculated from $g(S_o) \times dS_o/dM$. The results described elsewhere [9] enabled the value of dS_o/dM to be obtained from differentiation of the relation (obtained by the method of least squares) between S_o and M. This value was then utilised to calculate the curve for $g(M)$ against M.

Results and Discussion

The resultant molecular-weight distribution curves for the original glycogen (curve 1), the intermediate dextrin at 13% conversion into maltose (curve 2), and the β-limit dextrin (curve 3) are shown in the Figure. (It should be noted that these curves are weight- and not number-distributions.) Although the original glycogen was subfractionated, it still possessed a very wide distribution—from about 1×10^6 to about 13×10^6—illustrating the difficulties inherent in obtaining sharp fractions of glycogen.[9]

Molecular-weight distribution curves obtained by the above methods are not absolute unless ideal polymers which are molecularly homogeneous are available: the form of the $g(S)$–S curve depends entirely on the relation between S and c, and this can be influenced

by heterogeneity in molecularity. Also the transformation of the $g(S)$–S curve into the $g(M)$–M curve depends on $S = f(M)$, and this relation presents several difficulties experimentally when non-ideal samples are used: heterogeneous molecularity may influence the results, and there are often inaccuracies in measurements of the diffusion coefficients. [The method suggested by Williams and Saunders [4] for combining sedimentation-equilibrium and -velocity measurements appears to have many advantages in that diffusion measurements are avoided by using a double plot of integral distribution of M (from equilibrium measurements) and S (from velocity measurements).] For our calculations, we used the relation previously obtained [21] of $S_{20} = (S_{20})_0(1 - kc)$. Other results [9] have indicated that $dS/dM = (4{\cdot}79 \times 10^{-25})S^{-0{\cdot}59}$. The latter equation is necessarily not extremely accurate, but is as good as can be expected.[9] It would appear that an *absolute* molecular-weight distribution is not yet available by this method. However, the distributions obtained here are satisfactory for comparisons on a molecular basis of



Molecular-weight distribution curves.

1, *Original glycogen.*
2, *Intermediate dextrin.*
3, *β-Limit dextrin.*
4, *Theoretical curve for β-limit dextrin (see text).*
5, *Theoretical curve for intermediate dextrin (see text).*

various types of degradation processes. (Since Larner and his co-workers [7] used different equations, no direct comparison is possible between the shapes of his distribution curves and those reported here.)

Mode of Action of the β-Amylase.—Although an accurate estimate of the enzyme concentration in these digests was not possible,[22] conditions were such that the substrate : enzyme ratio was high. The action pattern of the enzyme was investigated by comparing theoretical distributions calculated from the original for various mechanisms with those experimentally determined for the intermediate and limit dextrin. This was achieved by dividing the distribution curve into about 20 lamellæ of discrete molecular weight, and regarding each of these as a homogeneous polymer. If the attack of the β-amylase is random with regard to molecular size, then the decrease in molecular weight during β-amylolysis will be proportional to the number of non-reducing terminal units, *i.e.*, to the molecular weight, and the molecular-weight distribution for the limit dextrin (M_{LD}) will be simply related to that of the original (M_O) by $M_{LD} = (100 - c)M_O/100$, where c = the percentage conversion into maltose (*i.e.*, 41%).

Curve 4 is the result of such a calculation. Comparison with the experimental curve (3) shows agreement within experimental error. It appears that it is essentially correct that all glycogen molecules are degraded to the same relative extent after β-amylolysis; there is no appreciable preferential and more extensive degradation of material of either low or high molecular weight.

[21] Bryce, Greenwood, Jones, and Manners, *J.*, 1958, 711.
[22] Banks and Greenwood, unpublished experiments.

For the intermediate dextrin, a theoretical curve was first calculated on the assumption that 32% of the molecules over the whole molecular-weight range were converted to the limit of 41% of maltose (*i.e.*, the percentage necessary to account for the observed limit of 13%), while the remainder were unchanged. However, although the maximum in the resultant distribution was correct, the high-molecular-weight leading edge was very much higher than the experimental curve, and the amount of material in the molecular-weight range of 3—6 $\times$ 10^6 was too low, the differences in each case being outside experimental error. This mechanism was therefore not compatible with the experimental results. However, when the theoretical curve (curve 5) was calculated by assuming a 13% conversion of all molecular species, good agreement was obtained with the experimental curve. This suggests that during β-amylolysis, all glycogen molecules are degraded to the same extent independently of molecular size, and the enzyme does not in fact degrade one molecule completely before attacking another. Rather it appears that action must be random with regard to individual external chains. This is in agreement with unpublished kinetic experiments carried out by Mr. W. Banks. First-order kinetics are virtually non-existent, being obeyed for only the first 10% of the total reaction, and thereafter there is a gradual decrease in rate. This suggests that as β-amylolysis progresses, it becomes increasingly more difficult to remove successive maltose units from any chain; such a mechanism implies that essentially all molecules will be degraded to the same extent throughout the reaction.

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DEPARTMENT OF CHEMISTRY, THE UNIVERSITY,
EDINBURGH, 9.

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715. *The Cationic Oligomerisation * of the Stilbenes.*

By D. S. BRACKMAN and P. H. PLESCH.

Oligomerisation of *trans*-stilbene in benzene–hexane catalysed by titanium tetrachloride and trichloroacetic acid together is a cationic chain-reaction yielding a mixture of dimers and trimers which are substituted indanes. In toluene *trans*-stilbene gives about 50% of indane dimer and 50% of 1 : 2-diphenyl-1-*p*-tolylethane; *cis*-stilbene forms the latter almost exclusively. The rate of oligomerisation of *trans*-stilbene in benzene–hexane is of the first order in monomer and of a complex order in catalyst and co-catalyst. In *n*-hexane at 0° *cis*-stilbene gives a mixture of oligomers up to and including a pentamer: the initiating species, a complex between catalyst and co-catalyst, is involved in an equilibrium which complicates the interpretation of rate constants and activation energies.

THE scanty literature on the oligomerisation of the stilbenes contains no kinetic studies. A dimer of *trans*-stilbene was prepared photochemically [1,2] and identified as 1 : 2 : 3 : 4-tetraphenyl*cyclo*butane.[2,3] The free-radical homopolymerisation of the stilbenes has not been reported, although some copolymers have been prepared. A solution of potassium amide in liquid ammonia does not polymerise *trans*-stilbene.[4] Studies of the polymerisation of *trans*-stilbene by aluminium chloride in carbon disulphide [5,6] indicated

* The term oligomer is used to denote low polymers, up to decamers.

[1] Ciamician and Silber, *Ber.*, 1902, **35**, 4128.
[2] Pailer and Müller, *Monatsh.*, 1948, **29**, 615.
[3] Fulton and Dunitz, *Nature*, 1947, **160**, 161.
[4] Wooding, Thesis, Leeds, 1950.
[5] Liebermann and Mitter, *Ber.*, 1912, **45**, 1212.
[6] Scholl and Schwarzer, *Ber.*, 1922, **55**, 324.

that at most a trimer was formed. Qualitative observations on the reactions of the stilbenes in the presence of boron fluoride, titanium tetrachloride, and sulphuric and trichloroacetic acid have been reported,[7] and the oligomerisations of the stilbenes in boron fluoride–ether [8] and of *trans*-stilbene in antimony trichloride [9] have also been studied. The present work deals with the oligomerisation of *cis*- and *trans*-stilbene with titanium tetrachloride as catalyst and trichloroacetic acid as co-catalyst.

Experimental

Materials.—Hexane and solutions of titanium tetrachloride and trichloroacetic acid in it were prepared as described earlier.[10] Spectroscopically pure *n*-hexane was prepared by treating technical hexane with fuming sulphuric acid. Benzene was purified by standard methods and stored over phosphoric oxide. Toluene was repeatedly shaken with concentrated sulphuric acid, decanted, refluxed for 1 hr. with aluminium chloride, and distilled; 75% distilled at 109—110°. The distillate was shaken with dilute aqueous sodium hydroxide and with water, dried (K_2CO_3), refluxed with sodium, and distilled through a 60 cm. Vigreux column with a reflux ratio of 10 : 1. More than 75% distilled over a range of 0·4°, and was stored over phosphoric oxide. *cis*- and *trans*-Stilbene were prepared and purified as described earlier.[7,11]

Apparatus and Procedure.—The reaction vessel used for the isothermal experiments was a 50 ml. Pyrex flask fitted, by ground joints, with necessary inlets and a device by means of which samples of known volume could be removed from the reaction mixture at intervals for analysis, without admission of laboratory air. A weighed quantity of stilbene was introduced into the reaction vessel, the solvent (benzene) and the catalyst solution (titanium tetrachloride in hexane) were then added, and the co-catalyst solution (trichloroacetic acid in hexane) was run into a side-arm. It was necessary to use benzene as solvent since *trans*-stilbene is only very sparingly soluble in hexane. The benzene : hexane ratio varied from 2·2 to 0·77 by volume in the kinetic experiments and had no effect on the reaction rate. The vessel was kept in a thermostat-bath and when temperature equilibrium had been attained the co-catalyst and the monomer solution were mixed by tilting the vessel; samples of the reaction mixture were withdrawn at known time intervals. In the earlier experiments these samples were treated with aqueous sodium carbonate to remove catalyst and co-catalyst, the solvent was removed at about 60° under slightly reduced pressure, and unchanged monomer removed by heating the sample in a tared weighing bottle in a boiling-water bath under a high vacuum for 30 min. The quantity of oligomer left in the weighing bottle was found by weighing. With standardised technique satisfactory reproducibility was obtained. Thus the progress of the reaction with time was followed by direct weighing of the oligomer formed. In the later experiments the progress of the reaction was followed by determining the residual stilbene spectrophotometrically.

For the adiabatic experiments a stoppered Dewar vessel fitted with breakable phials, inlets, stirrer, electric heater, and a thermometer reading to 0·1° was used. The solid *trans*-stilbene and a solution of trichloroacetic acid in benzene were contained in breakable phials immersed in the solvent (benzene). The titanium tetrachloride was added as a solution in benzene. The co-catalyst phial, and subsequently the monomer phial, were broken, and the reaction thus started was followed by taking temperature readings at half-minute intervals.

Preliminary experiments showed that the oligomerisation of the stilbenes by titanium tetrachloride is fairly insensitive to traces of moisture, so that a rigorously anhydrous technique was not necessary. All reagents were handled, and the reaction mixture was kept, under dry nitrogen.

Some of the oligomers were roughly fractionated in a horizontal temperature gradient under a high vacuum. Molecular weights were determined cryoscopically in *cyclo*hexane or ebullioscopically in carbon tetrachloride. Hydrogenations were carried out in glacial acetic acid with a platinum oxide catalyst.

[7] Brackman and Plesch, *J.*, 1953, 1289.
[8] Price and Berti, *J. Amer. Chem. Soc.*, 1954, **76**, 1219.
[9] Porter and Baughan, *J.*, 1958, 744.
[10] Plesch, *J.*, 1950, 543.
[11] Brackman and Plesch, *J.*, 1952, 2188.

Results

In all the systems investigated the mixture of *trans*-stilbene and titanium tetrachloride was reddish-brown; when *cis*-stilbene was used the solutions were pale red. On addition of the trichloroacetic acid the colour did not change immediately, but faded to a pale yellow as the reaction progressed. The solutions were perfectly clear throughout, and there was no optical indication of heterogeneity, nor were deposits formed. The yield of the oligomerisations of *cis*- and *trans*-stilbene at 25° in hexane–benzene was 100% in every experiment which was allowed to go to completion. When a reaction had ceased through exhaustion of the monomer, a further portion of monomer added to the same reaction mixture, even several hours later, oligomerised readily. At temperatures above 50° the reactions did not go to completion. It was ascertained that this was not due to a monomer–oligomer equilibrium but the cause is still obscure, though there are indications that it may be due to a slow decomposition of the trichloroacetic acid.

Structure of the Oligomers.—The oligomerisation of *trans*- and *cis*-stilbene in hexane–benzene gave transparent resins, usually colourless but occasionally pale yellow, with an indefinite softening point between 50° and 80°. The molecular weights of all products were less than 1000. Since yields greater than 100% were never found, although specifically looked for, alkylation of benzene by stilbene cannot be an important reaction under the conditions of these experiments.

Theoretically, stilbene could form the following dimers without rupture of a C–C bond: (I) 1 : 2 : 3 : 4-tetraphenylbut-1-ene; (II) 1 : 2 : 3 : 4-tetraphenylbut-2-ene; (III) 1-benzyl-1 : 2-diphenylindane; (IV) 1-benzyl-2 : 3-diphenylindane; (V) 9 : 10-dihydro-9-(1 : 2-diphenylethyl)phenanthrene; (VI) 1 : 2 : 3 : 4-tetrahydro-1 : 2 : 3-triphenylnaphthalene; (VII) 1 : 2 : 3 : 4-tetraphenyl*cyclo*butane; (VIII) 4-(1 : 2-diphenylethyl)stilbene; (IX) cyclised derivatives of (VIII).

The trimers and higher members of the series would be: (*a*) Straight-chain, phenyl-substituted alk-1-enes or alk-2-enes analogous to (I) and (II); (*b*) indanes analogous to (III) and (IV) with phenylated *n*-propyl, *n*-pentyl, etc., groups in place of the benzyl group; (*c*) dihydrophenanthrenes analogous to (V), with phenylated *n*-butyl, *n*-hexyl, etc., groups in place of the phenylated ethyl group; (*d*) although no higher analogues of (VI) or (VII) are possible, macrocyclic rings could be formed, *e.g.*, by *para*-cyclisation; (*e*) higher oligomers involving structures similar to (VIII).

The oligomers produced from *trans*-stilbene in hexane–benzene were hydrocarbons [Found: C, 93·75, 93·2; H, 6·95, 6·85. $(C_{14}H_{12})_n$ requires C, 93·3; H, 6·7%]. The molecular weights were in the range 350—600 (Calc. for $C_{14}H_{12}$: *M*, 180·2). The ultraviolet spectrum showed a single strong peak near 2650 Å and, in some specimens, a low peak near 3000 Å which was removed by hydrogenation. Comparison with the spectrum of *trans*-stilbene showed that there was not more than 10 mole % of the unsaturation (which may have been due to residual *trans*-stilbene). This evidence eliminates structures (I) and (II), and also (V) which would have given an absorption resembling that of diphenyl. Structure (VII) was eliminated by comparison of the infrared spectra with that of an authentic sample obtained by courtesy of Dr. E. Bergmann. Structures (VIII) and (IX) are eliminated because the infrared spectra showed no trace of *para*-substitution. The infrared spectra of all the oligomers were similar, and almost unchanged by hydrogenation; they showed a great resemblance to that of polystyrene. One prominent feature is a strong band at 750 cm.$^{-1}$, easily distinguished from another at 760 cm.$^{-1}$, and not present in the spectrum of polystyrene. A detailed comparison with the infrared spectra of various substituted indanes and tetrahydronaphthalenes, and also chemical analogy with the formation of indane dimers from α-methylstyrene [12] and styrene,[13] all suggest that the stilbene oligomer is most probably a mixture of the dimer 1-benzyl-2 : 3-diphenylindane and of the corresponding trimer, 1 : 2-diphenyl-3-(1 : 2 : 3-triphenyl-*n*-propyl)indane. It should be noted that the dimer can exist in four geometrically isomeric forms.

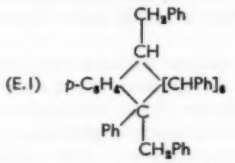
Oligomerisation of *trans*-stilbene in toluene gave a product which was separated by high-vacuum distillation into two approximately equal fractions. The less volatile compound (A) consisted mainly of a dimer (Found: *M*, 390; C, 93·2; H, 7·0%) having ultraviolet and infrared spectra similar to those of the oligomer formed in hexane–benzene. The other fraction (B)

[12] Dainton and Tomlinson, *J.*, 1953, 151.
[13] Corson, Dorsky, Nickels, Kutz, and Thayer, *J. Org. Chem.*, 1954, **19**, 17.

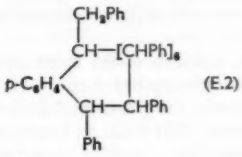
crystallised slowly; after three recrystallisations from ethanol it melted at 42—43°. It was identified by two syntheses as 1 : 2-diphenyl-1-*p*-tolylethane.[14]

Oligomerisation of *cis*-stilbene in toluene gave a single product, which was proved identical with product (B) by refractive index, m. p. and mixed m. p., and infrared spectrum.

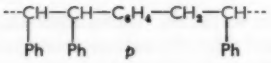
The oligomerisation of *cis*-stilbene in *n*-hexane at 0° yielded a product which was separated by high-vacuum distillation into components (C), b. p. 150—160° (*M*, 434), and (D), b. p. 250—270° (*M*, 566), and a residue (E) (*M*, 923) (Calc. for dimer: *M*, 360; for trimer, *M*, 540; for pentamer, *M*, 900). Fraction (C) absorbed about 0·3 mol. of hydrogen, (E) absorbed none. The ultraviolet spectra of all three fractions showed no absorption above 2850 Å, indicating substantial absence of double bonds conjugated with benzene rings. The infrared spectra of fractions (C) and (D) were generally similar to those of the oligomers obtained from *trans*-stilbene in benzene. However, the spectrum of fraction (E) showed strong evidence for *para*-substitution (bands at 825, 1020, 1510, 1890 cm.$^{-1}$); in addition, there is a strong broad band near 745 cm.$^{-1}$, but the band at 760 cm.$^{-1}$ is absent, and instead there is a shoulder on the 745 cm.$^{-1}$ band indicating a strong band near 730 cm.$^{-1}$; other distinctive features of this spectrum are strong bands at 955 and 1420 cm.$^{-1}$. The whole evidence is consistent with a macrocyclic structure formed by *para*-cyclisation, such as (E.1) or (E.2).



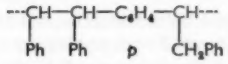
(E.1)



(E.2)



(E.3)



(E.4)

Another possibility is that a benzene ring is included in the chain by " perverse " propagation,[15] leading to the structures (E.3) or (E.4).

Kinetics.—trans-*Stilbene.* Adding titanium tetrachloride to a solution of *trans*-stilbene in hexane–benzene generally produced no reaction, or only a very slow one, indicating that co-catalysis by adventitious moisture was not an important effect. Adding the trichloroacetic acid solution to such a quiescent mixture induced an immediate reaction, as shown by the typical conversion–time curves in Fig. 1.

The early work (reported previously in outline [16]) indicated that a large part, in some cases up to 60%, of the reaction proceeded at nearly constant rate. However, repetition of some of these experiments with the much more sensitive spectroscopic technique indicated that the reactions were of first order with respect to monomer, suggesting that the approximate constancy of the rates found in many of the earlier experiments was an artefact. It was found later that most of the earlier experiments gave good first-order plots. In most of the experiments the oligomerisation was of the first order with respect to monomer up to more than 70%, and in some experiments to over 90%, conversion. From the logarithmic plots, examples of which are shown in Fig. 2, the first-order rate constants k_1 were obtained; as shown in Table 1, k_1 was independent of the monomer concentration. The dependence of k_1 at 25° on co-catalyst concentration is shown in Table 2 and Fig. 3, and its dependence on the catalyst concentration at 25° is shown in Table 3 and Fig. 4. The rate of oligomerisation is given by

$$-\mathrm{d[M]}/\mathrm{d}t = k_1[\mathrm{M}] = k_2[\mathrm{M}][\mathrm{HX}]$$

where M = monomer and HX is a complex of titanium tetrachloride and trichloroacetic acid. the nature of which will be discussed below. In the earlier report,[16] it had also been stated erroneously that the rate varied as $[\mathrm{M}]^2$.

The adiabatic experiments (Table 4) carried out with very large concentrations of catalyst and co-catalyst in order to get fast reactions, also gave good first-order plots.

[14] Brackman and Plesch, *Chem. and Ind.*, 1955, 255.
[15] Plesch, *J.*, 1953, 1662.
[16] Brackman and Plesch, in " Cationic Polymerisation and Related Complexes," Ed. P. H. Plesch, W. Heffer and Sons, Cambridge, 1953, p. 103.

The dependence of k_1 on temperature is shown in Table 5 and the activation energy in Table 7.

The oligomerisation of *trans*-stilbene in toluene gave, as mentioned above, a mixture of oligomers and of 1 : 2-diphenyl-1-*p*-tolylethane. The rate of consumption of stilbene was of first order with respect to stilbene. The kinetics of this system were not investigated in detail because it involved two simultaneous reactions.

Results obtained on the oligomerisation of *trans*-stilbene in pure *n*-hexane are shown in Table 5.

FIG. 1.

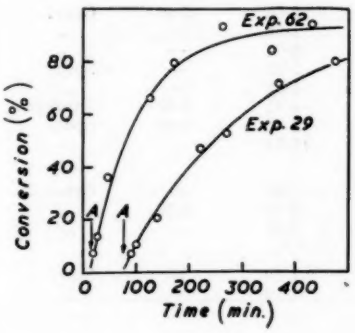


FIG. 2.

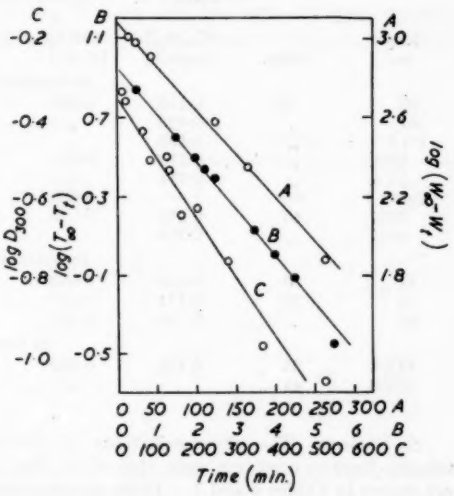


FIG. 1. *Typical time–conversion curves for the oligomerisation of* trans-*stilbene in benzene–hexane at* 25°.
The titanium tetrachloride was added at time = 0, and the trichloroacetic acid at the time marked *A*.
Expt. 29: $[C_{14}H_{12}] = 0{\cdot}16$, $[TiCl_4] = 0{\cdot}082$, $[CCl_3{\cdot}CO_2H] = 0{\cdot}019$ mole/l.
A = 72 min. $k_1 = 6{\cdot}9 \times 10^{-5}$ sec.$^{-1}$.
Expt. 62: $[C_{14}H_{12}] = 0{\cdot}15$, $[TiCl_4] = 0{\cdot}20$, $[CCl_3{\cdot}CO_2H] = 0{\cdot}011$ mole/l.
A = 15 min. $k_1 = 1{\cdot}7 \times 10^{-4}$ sec.$^{-1}$.

FIG. 2. *First-order plots for the oligomerisation of* trans-*stilbene at* 25°.
A, Gravimetric: $(W_\infty - W_t)$ is the mass of monomer remaining at time *t*.
B, Adiabatic: T_t is the temperature at time *t* and T_∞ the final temperature, corrected for cooling.
C, Spectroscopic: D_{300} is the optical density at 300 mμ at time *t*, due to absorption by the *trans*-stilbene.
A: Expt. 62, see Fig. 1.
B: Expt. 134, see Table 4.
C: $[C_{14}H_{12}] = 0{\cdot}10$, $[TiCl_4] = 0{\cdot}080$, $[CCl_3{\cdot}CO_2H] = 0{\cdot}010$ mole/l.

TABLES 1—3. *Oligomerisation of* trans-*stilbene at* 25°.

(1) $[TiCl_4] = 0{\cdot}08$ mole/l. $[CCl_3{\cdot}CO_2H] = 0{\cdot}01$ mole/l.

$[C_{14}H_{12}]$ (mole/l.)	0·052	0·127	0·186	0·21	0·23	0·25	0·273
$10^5 k_1$ (sec.$^{-1}$)	3·99	2·50	4·37	4·44	4·74	4·09	2·63

Average k_1 3·82 × 10^{-5} sec.$^{-1}$. Standard deviation 24%.

(2) $[C_{14}H_{12}] = 0{\cdot}15$ mole/l. (*A*) $[TiCl_4] = 0{\cdot}20$ mole/l.

$10^2[CCl_3{\cdot}CO_2H]$ (mole/l.) ...	0·58	0·78	1·41	1·81	1·80	2·40	2·45	3·13
$10^5 k_1$ (sec.$^{-1}$)	3·93	6·54	13·0	21·9	16·0	33·0	30·0	31·8

(*B*) $[TiCl_4] = 0{\cdot}084$ mole/l.

$10^2[CCl_3{\cdot}CO_2H]$ (mole/l.) ...	0·10	0·39	0·50	0·97	1·65	1·88	3·39	3·70
$10^5 k_1$ (sec.$^{-1}$)	0·32	1·36	3·08	2·30	5·15	6·88	7·50	8·06

(3) $[C_{14}H_{12}] = 0{\cdot}15$ mole/l. $[CCl_3{\cdot}CO_2H] = 0{\cdot}012$ mole/l.

$10^2[TiCl_4]$ (mole/l.)	1·04	3·6	6·4	9·6	14·6	19·0
$10^5 k_1$ (sec.$^{-1}$)	1·16	2·72	4·75	9·45	11·02	11·22

TABLE 4. *Adiabatic oligomerisation of* trans-*stilbene at* 20—25° *in benzene.*

Expt. no.	132	127	135	116	119	134
$[C_{14}H_{12}]$ (mole/l.)	0·153	0·294	0·300	0·367	0·432	0·452
$[TiCl_4]$ (mole/l.)	0·397	0·386	0·385	0·376	0·376	0·376
$[CCl_3{\cdot}CO_2H]$ (mole/l.)	0·063	0·061	0·061	0·091	0·060	0·060
10^5k_1 (sec.$^{-1}$)	9·10	9·46	8·89	9·64	10·15	9·38

Average $k_1 = 9{\cdot}27 \times 10^{-5}$ sec.$^{-1}$.

TABLE 5. *Oligomerisation of* trans-*stilbene.*

Exp. no.	Temp.	$[C_{14}H_{12}]$ (mole/l.)	$[TiCl_4]$ (mole/l.)	$[CCl_3{\cdot}CO_2H]$ (mole/l.)	10^5k_1 (sec.$^{-1}$)	Average 10^5k_1 (sec.$^{-1}$)	Method
			In benzene–hexane				
92	0°	0·116	0·080	0·010	3·66	2·46	Grav.
91	,,	0·125	,,	,,	1·66	—	,,
101A	,,	0·193	,,	,,	3·05	—	,,
3NA	,,	0·210	0·075	0·0094	2·31	—	Spec.
5NA	,,	0·214	,,	,,	1·62	—	,,
Table 1	25	—	0·080	0·010	3·92	3·92	Average
3NC	45	0·210	0·075	0·0094	5·72	5·98	Spec.
5NC	,,	0·214	,,	,,	6·24	—	,,
			In toluene–hexane				
33	0	0·120	0·050	0·0118	1·00	—	Grav.
25	25	0·144	0·050	0·0117	3·59	3·30	,,
65	,,	0·194	0·087	0·0097	3·01	—	,,
			In hexane				
10NA	25	0·122	0·080	0·010	1·18	—	Spec.
10NB	45	,,	,,	,,	1·70	—	,,

cis-*Stilbene.* The oligomerisations of *cis*-stilbene in hexane–benzene, pure hexane, and toluene–hexane mixtures were also of the first order with respect to monomer. The results are shown in Tables 6 and 7. These systems were not investigated in detail.

TABLE 6. *Oligomerisation of* cis-*stilbene.*

$[TiCl_4] = 0{\cdot}08$ mole/l. $[CCl_3{\cdot}CO_2H] = 0{\cdot}01$ mole/l.

No.	$[C_{14}H_{12}]$ (mole/l.)	10^5k (sec.$^{-1}$)	Average 10^5k_1 (sec.$^{-1}$)	Method	No.	$[C_{14}H_{12}]$ (mole/l.)	10^5k_1 (sec.$^{-1}$)	Average 10^5k_1 (sec.$^{-1}$)	Method
	In benzene–hexane at 0°					In benzene–hexane at 25°			
83	0·096	5·50	4·66	Grav.	79	0·109	7·47	7·16	Grav.
84	0·099	5·52	—	,,	76	0·118	9·28	—	,,
4NA	0·160	3·46	—	Spec.	4NB	0·130	5·34	—	Spec.
	In toluene–hexane at 0°					In toluene–hexane at 25°			
11NA	0·107	1·50	1·64	Spec.	11NB	0·107	3·25	3·06	Spec.
9NA	0·123	1·92	—	,,	9NB	0·123	2·09	—	,,
8NA	0·125	1·17	—	,,	8NB	0·125	2·86	—	,,
12NA	0·125	1·98	—	,,	12NB	0·125	3·97	—	,,
	In hexane					In hexane at 25°			
80	0·188 (18°)	0·0515	—	Grav.	7NB	0·128	5·88	4·91	Spec.
7NA	0·128 (0°)	1·65	—	Spec.	120	0·128	3·94	—	Grav.

TABLE 7. *Summary of kinetic results.*

	cis				*trans*		
Solvent	Temp.	Average 10^5k_1 (sec.$^{-1}$)	E * (kcal. mole^{-1})	Solvent	Temp.	Average 10^5k_1 (sec.$^{-1}$)	E * (kcal. mole^{-1})
C_6H_6–C_6H_{14}	0°	2·46	3·7	C_6H_6–C_6H_{14}	0°	4·66	2·8
	25	3·92			25	7·16	
	45	5·98		PhMe–C_6H_{14}	0	1·64	4·0
PhMe–C_6H_{14}	25	3·30			25	3·06	
				C_6H_{14}	25	4·91	

* Evaluated only when more than one result at each temperature is available.

Vol. 1958, page 3568, Table 7. Interchange the headings *cis* and *trans*.

Discussion

Our evidence concerning the oligomerisation of the stilbenes catalysed by titanium tetrachloride and trichloroacetic acid can be interpreted in terms of a cationic chain-reaction essentially similar to the oligomerisations and polymerisations of other olefins by similar systems. However, a detailed analysis of our results is made particularly awkward by the facts that, not only is the catalytic species produced by an equilibrium reaction between the catalyst and the co-catalyst, but the catalyst itself is undoubtedly involved in complex formation with the solvent (benzene) [17] and with the monomers.[7]

The Nature of the Initiator.—The plots in Fig. 3 show that the rate of oligomerisation of *trans*-stilbene is directly proportional to the concentration of trichloroacetic acid (AH)

Fig. 3.

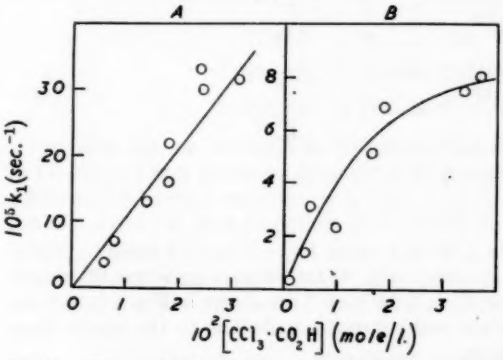


Fig. 4.

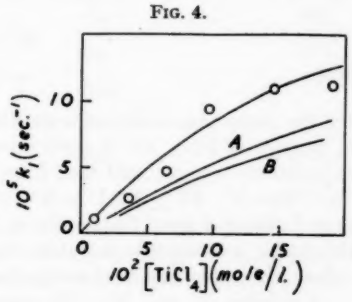


Fig. 3. *Oligomerisation of* trans-*stilbene in benzene–hexane. Dependence of first-order rate constant* k_1 *on concentration of trichloroacetic acid.*

Temp. 25°. Concn. of *trans*-stilbene 0·15 mole/l. Concn. of titanium tetrachloride: *A*, 0·20 mole/l.; *B*, 0·084 mole/l.

Fig. 4. *Oligomerisation of* trans-*stilbene in benzene–hexane. Dependence of first-order rate constant* k_1 *on concentration of titanium tetrachloride.*

Temp. 25°. Concn. of *trans*-stilbene 0·15 mole/l., concn. of trichloroacetic acid 0·012 mole/l. Line *A*, $K' = 5{\cdot}2$ l. mole^{-1}. Line *B*, $K = 0{\cdot}6$ l. mole^{-1}.

only when the titanium tetrachloride (C) is in considerable excess. This suggests that the initiating complex is involved in an equilibrium; four such equilibria suggest themselves:

$$(AH)_2 + 2C \rightleftharpoons 2C,AH \quad K \quad (a)$$
$$(AH)_2 + C \rightleftharpoons C,(AH)_2 \quad K' \quad (b)$$
$$(AH)_2 + 2C \rightleftharpoons C_2,(AH)_2 \quad K'' \quad (c)$$
$$(AH)_2 + 4C \rightleftharpoons 2C_2,(AH) \quad K''' \quad (d)$$

It will be shown below that only (*a*) and (*b*) need to be considered.

Calculation of K.—If a_0 and c_0 represent the nominal concentrations of trichloroacetic acid and titanium tetrachloride in the reaction mixture, and x the concentration of C,AH, then

$$K = 2x^2/(a_0 - x)(c_0 - x)^2$$

and

$$c_0 = x + x[2/K(a_0 - x)]^{0{\cdot}5} \quad (1)$$

When $c_0 \gg a_0$, virtually all the acid will be in the complex form, so that then $x = a_0$ (plot *A* of Fig. 3). We now assume that the rate of oligomerisation is given by

$-d[M]/dt = k_2[M]x$, and that for plot *A* of Fig. 3 $x = a_o$. Hence we find $k_2 = 1{\cdot}05 \times 10^{-2}$ l. mole^{-1} sec.$^{-1}$. Using this value we can calculate x, and hence K, for each point on curve *B* of Fig. 3, from the relation $k_1 = k_2x$, where now $x \neq a_o$. The mean K thus obtained, $0{\cdot}51 \pm 0{\cdot}26$ l. mole^{-1}, when combined with the mean K, $0{\cdot}72 \pm 0{\cdot}17$ l. mole^{-1}, derived in a similar manner from the data of Table 1, gives a weighted mean $K = 0{\cdot}60 \pm 0{\cdot}3$ l. mole^{-1}. (The limits of uncertainty indicated here and in the following section are standard deviations.)

As a test we can calculate the curve of Fig. 4. The obvious way of doing this, to calculate x, and hence k_1, for various values of c_o, would entail the solution of a cubic equation in x; this can be circumvented by calculating x for various conveniently chosen values of k_1, and then computing the corresponding c_o values from equation (1). The values thus obtained are shown by curve *B* in Fig. 4.

Calculation of K'.—Considering now the equilibrium (*b*) and denoting by y the concentration of the complex $C_2(AH)_2$, we obtain

$$K' = 2y/(a_o - y)(c_o - y)$$

and

$$c_o = 2y/K'(a_o - y) + y \quad \ldots\ldots\ldots \quad (2)$$

By the same arguments as were used in the calculation of K above, we can now find a $k_2' = k_1/y = 2{\cdot}1 \times 10^{-2}$ l. mole^{-1} sec.$^{-1}$ from plot *A* of Fig. 3, assuming that for this set of experiments $y = a_o$; and then from the data of curve *B* we calculate a set of values of K'. The mean K', $4{\cdot}7 \pm 1{\cdot}7$ l. mole^{-1}, thus obtained, when combined with $K' = 5{\cdot}7 \pm 1{\cdot}3$ l. mole^{-1} obtained from the results in Table 1, gives a mean $K' = 5{\cdot}2 \pm 2$ l. mole^{-1}. Using this value, we can now calculate the k_1–c_o curve (Fig. 4) for various conveniently chosen values of k_1; the results thus obtained for $K' = 5{\cdot}2$ l. mole^{-1} are shown in Fig. 4 (curve *A*).

Equilibria (c) and (d).—The appropriate computations analogous to the above show that these equilibria need not be considered.

Discrimination between Equilibria (a) and (b).—Neither the relative degree of constancy of K and K', nor the goodness of fit of the corresponding calculated k_1–c_o curves in Fig. 4, affords an unambiguous discrimination between equilibria (*a*) and (*b*), though both criteria favour (*b*).

Reaction Mechanism for trans-*Stilbene in Hexane–Benzene.*—The initiation reaction most probably involves a proton-transfer from the catalytic complex to the monomer:

$$HX + C_{14}H_{12} \longrightarrow Ph{\cdot}CH_2{\cdot}^{+}CHPh\ X^{-}$$

where HX represents the catalytic complex, $x = C_2AH$ or $y = C_2(AH)_2$: the resulting carbonium ion and complex anion must be associated as an ion-pair, in view of the very low dielectric constant of the solvent.

In the propagation step, the stilbene ion thus formed adds on to a stilbene molecule

$$Ph{\cdot}CH_2{\cdot}^{+}CHPh + C_{14}H_{12} \longrightarrow Ph{\cdot}CH_2{\cdot}CHPh{\cdot}CHPh{\cdot}^{+}CHPh$$

The fading of the brown-red colour of the solutions during the reaction indicates that the product does not contain double-bonds conjugated with a benzene ring; for, if it did, these would form coloured carbonium ions in the presence of the catalyst and co-catalyst and the colour of the solution would not change appreciably during the reaction. Moreover, the low molecular weight of the products indicates that chain transfer is a dominant reaction. Thus, after the first propagation step, two reaction paths are open to the " distilbene " ion: either it adds to another monomer molecule, or it undergoes cyclisation to a substituted indane by an intramolecular Friedel–Crafts reaction. The " tristilbene " ions only react by the second path, since the reaction products generally did not contain tetramers.

The indane-formation and proton-transfer reactions are probably closely associated because the indane is protonated when first formed, and then becomes " deactivated " by transferring the proton to a monomer molecule.

The fading of the colour of the reaction mixture during the reaction also shows that the carbonium ions disappear, which may indicate a regeneration of the catalytic complex:

$$H\cdot[C_{14}H_{12}]_n^+ X^- \longrightarrow [C_{14}H_{12}]_n + HX$$

where $n = 2$ or 3. These elementary reactions can be summarised in the following scheme which is similar to that of Dainton and Tomlinson:[12]

$$\left.\begin{aligned} 2C + (AH)_2 &\rightleftarrows C,AH \\ \text{or}\quad C + (AH)_2 &\rightleftarrows C,(AH)_2 \end{aligned}\right\} = HX \qquad \begin{aligned} &K \quad (ia) \\ &K' \quad (ib) \end{aligned}$$

$$HX + M \longrightarrow HM^+X^- \qquad k_i \quad (ii)$$

$$HM^+X^- + M \longrightarrow HM_2^+X^- \qquad k_{p1} \quad (iii)$$

$$HM_2^+X^- + M \longrightarrow HM_3^+X^- \qquad k_{p2} \quad (iv)$$

$$HM_2^+X^- + M \longrightarrow M_2 + HM^+X^- \qquad k_{m2} \quad (v)$$

$$HM_3^+X^- + M \longrightarrow M_3 + HM^+X^- \qquad k_{m3} \quad (vi)$$

$$HM_2^+X^- \longrightarrow M_2 + HX \qquad k_{t2} \quad (vii)$$

$$HM_3^+X^- \longrightarrow M_3 + HX \qquad k_{t3} \quad (viii)$$

If it be assumed that (*a*) the formation of complexes by titanium tetrachloride with benzene [17] and with *trans*-stilbene [7] does not affect the rate of reaction, (*b*) reactions (v) and (vi) do not affect the rate of reaction, and (*c*) the stationary state hypothesis is applicable in the form:

$$d[HM^+X^-]/dt = d[HM_2^+X^-]/dt = d[HM_3^+X^-]/dt = 0$$

it follows that

$$-\frac{d[M]}{dt} = k_i[M][HX]\left[2 + \frac{k_{p2}[M]}{k_{p2}[M] + k_{t2}}\right]$$

This agrees with the experimental rate law

$$-d[M]/dt = k_2[M][HX] \qquad (3)$$

if $k_{p2}[M] \approx k_{t2}$, which is not unreasonable. It follows that $k_i = k_2/2{\cdot}5 = 4{\cdot}2 \times 10^{-3}$ l. mole^{-1} sec.$^{-1}$ at 25°. It should be noted, however, that other reaction schemes could account for the observed rate law, and these would lead to different interpretations of k_2.

If the rate of reaction is given by

$$-d[M]/dt = 2{\cdot}5\, k_i[M][HX]$$

and [HX] is given either by x of eqn. (1) or by y of eqn. (2), the activation energy $E = f(E_i, \Delta H)$, where E_i is the activation energy of reaction (ii) and ΔH the heat of reaction (*a*) or (*b*) on p. 3569; thus f cannot be evaluated in any useful manner and E cannot be interpreted explicitly.

The question arises why no high polymers are formed in this reaction. The reason is not thermodynamic, because polystilbenes of high molecular weight can be made at ambient temperatures by polymerisation of phenyldiazomethane; moreover, models confirm that steric hindrance is not excessive. The reason must therefore be kinetic, *i.e.*, after formation of the trimer the cyclisation reaction becomes very much faster than the propagation.

[17] Cullinane, Chard, and Leyshon, *J.*, 1952, 4106.

Adiabatic Experiments.—The experiments recorded in Table 4 indicate that the rate law (3) does not apply when relatively large concentrations of catalyst and co-catalyst are used; this is particularly evident from a comparison of expt. 116 with the others: a 50% increase in the concentration of co-catalyst did not alter k_1. Moreover, if we applied this same rate law and took as an approximation [HX] = [CCl_3·CO_2H], k_2 would be of the order of 0·15 l. mole^{-1} sec.$^{-1}$, *i.e.*, about fifteen times as great as the k_2, or seven times the k_2' derived from the isothermal experiments. In view of the complexity of the system we cannot offer a plausible explanation for this phenomenon.

Oligomerisation of cis-*Stilbene in Benzene–Hexane.*—For the oligomerisation of *cis*-stilbene the first-order rate constant k_1 is greater, and the experimental activation energy E is smaller, than for *trans*-stilbene (Table 7). It follows from our kinetic analyses that the difference between the experimental activation energies for the oligomerisation of the two isomers, $E^c - E^t = \Delta E = -0{\cdot}9$ kcal., is equal to ΔE_i, the difference between the activation energies of the initiation reactions. ΔE_i can be correlated with the difference between the resonance energies, ΔE_{Res}, of the isomers (−4·7 kcal.), as in Fig. 5. This shows that for the addition of a proton to the double bond the difference between the resonance energies of the transition states, $\Delta E_{Res}^{\ddagger}$, is equal to $\Delta E_{Res} - \Delta E_i = -3{\cdot}8$ kcal. $\Delta E_{Res}^{\ddagger}$ is smaller than ΔE_{Res} because for *cis*-stilbene in the proton-addition transition state the steric inhibition of resonance is smaller than in the initial state.

If A_i^c and A_i^t are the Arrhenius pre-exponential factors of the initiation reaction for the *cis*- and the *trans*-isomers

$$\log (A_i^c/A_i^t) = \log (k_1^c/k_1^t) + \Delta E/RT$$

From the data of Table 7 we find that $A_i^c/A_i^t = 10$ at 0° and 8·4 at 25°, indicating that the *cis*-isomer is more accessible for proton addition than the *trans*-isomer. Thus, the greater reaction rates obtained with *cis*-stilbene are at least partly due to both a higher A factor and a lower activation energy in the initiation.

Oligomerisation of trans- *and* cis-*Stilbene in Toluene.*—The alkylation concurrent with the oligomerisation, which produces the 1 : 2-diphenyl-1-*p*-tolylethane, is closely analogous to the alkylation of toluene by the polystyrene ion, discovered by Plesch [18] and investigated by Endres and Overberger [19] and by Higashimura and Okamura.[20]

The fact that *trans*-stilbene yields about 50% of oligomer and 50% of 1 : 2-diphenyl-1-*p*-tolylethane, whereas *cis*-stilbene gives the latter exclusively, indicates that reactivity towards the stilbene cation is steeply graded in the order *trans*-stilbene > toluene > *cis*-stilbene. From our results we can estimate that the rate of reaction of a stilbene ion with *trans*-stilbene is at least a hundred times as great as the rate of its reaction with *cis*-stilbene. If we assume that for these two propagation reactions the ratio of the A factors, A_p^c/A_p^t, is the same as for the initiation, we find that the activation energy, E_p, of this propagation reaction is about 4 kcal. greater for *cis*- than for *trans*-stilbene. Overberger's suggestion [21] that this is due to the steric inhibition of resonance in the transition state for *cis*-stilbene is certainly valid, but is insufficient to account for the fact, illustrated in Fig. 6, that on our present hypothesis the transition state for carbonium-ion addition would lie at a level which is about 9 kcal., *i.e.*, ($\Delta E_{Res} + \Delta E_p$), higher for *cis*- than for *trans*-stilbene. This difference is almost twice as great as ΔE_{Res}; it may be symptomatic of differences in the transition states derived from the two isomers involving the stabilisation (positive or negative) of the carbonium ion, or the Coulombic energy arising from interaction with the anion X^-.

Oligomerisation of trans- *and* cis-*Stilbene in* n-*Hexane.*—The oligomerisation of both isomers in hexane is significantly slower than in solvents containing benzene or toluene.

[18] Plesch, *J.*, 1953, 1659.
[19] Endres and Overberger, *J. Amer. Chem. Soc.*, 1955, **77**, 2201; *J. Polymer Sci.*, 1955, **16**, 283.
[20] Higashimura and Okamura, *J. High-Polymer Chem.* (*Japan*), 1956, **13**, 397.
[21] Overberger, ref. 16, p. 105.

The small difference in the dielectric constants cannot account for this difference between aliphatic and aromatic solvents which is by no means unique. Probably it is attributable to the much higher polarisability of the aromatic solvents in virtue of which solvation of polar species, in particular the transition-state complex, is much stronger, and consequently the activation energy smaller, than in aliphatic solvents. The ion-pairs will be surrounded (solvated) by the most polar or polarisable molecules available, and in hexane solution this is the monomer; thus the formation from *cis*-stilbene of oligomers up to pentamer in hexane at 0°, but not in benzene–hexane, is understandable.

Conclusion.—In the field of cationic polymerisation the isomeric stilbenes provide an opportunity for comparative structural and kinetic studies, and are worthy of further

FIG. 5.

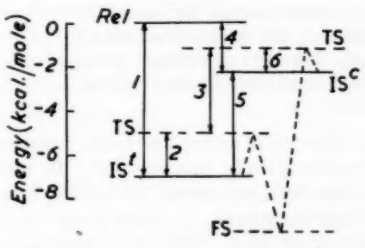


FIG. 6.

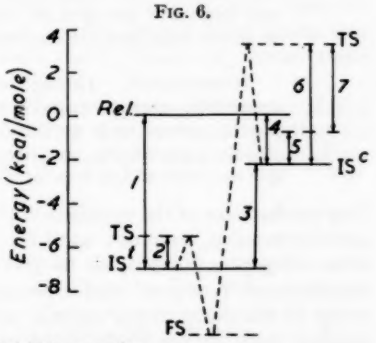


FIG. 5. *Energy-level diagram for the initiation reaction.*

The reference energy level represents the energy of the hypothetical stilbene molecule devoid of resonance interaction between the benzene rings and the double bond, plus the energy of the initiating complex HX. The energy levels shown by broken lines are indeterminate. The sloping broken lines indicate the reaction path.

REL = Reference energy level. TS = Transition state.
IS^t = Initial state, *trans*-$C_{14}H_{12}$ + HX.
IS^c = Initial state, *cis*-$C_{14}H_{12}$ + HX.
FS = Final state, $C_{14}H_{13}^+X^-$.

1, $E^t_{Res} = 7{\cdot}0$. 2, E^t_i. 3, $\Delta E_{Res}{}^{\ddagger}$. 4, $E^c_{Res} = 2{\cdot}3$. 5, $\Delta E_{Res} = 4{\cdot}7$. 6, $E^c_i = E^t_i - 0{\cdot}9$. (All units kcal./mole.)

FIG. 6. *Energy-level diagram for the propagation reaction.*

The reference energy level has the same significance as in Fig. 5 but with the stilbene ion $C_{14}H_{13}^+$ in place of HX. The significance of the broken lines is the same as in Fig. 5.

REL = Reference energy level. TS = Transition state.
IS^t = Initial state, *trans*-$C_{14}H_{12} + C_{14}H_{13}^+$.
IS^c = Initial state, *cis*-$C_{14}H_{12} + C_{14}H_{13}^+$.
FS = Final state, $C_{28}H_{25}^+$.

1, $E^t_{Res} = 7{\cdot}0$. 2 and 5, E^t_p. 3, $\Delta E_{Res} = 4{\cdot}7$. 4, $E^c_{Res} = 2{\cdot}3$. 6, E^c_p. 7, $\Delta E_p = 4$. (All units are kcal./mole.)

investigation. The dual catalytic system chosen by us many years ago when this work was started is not very suitable for kinetic work because of its intrinsic complexity, but the salt-like catalysts recently described [22] should prove useful also in this field.

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MANCHESTER UNIVERSITY.
UNIVERSITY COLLEGE OF NORTH STAFFORDSHIRE,
KEELE, STAFFORDSHIRE.

[*Received, May 2nd,* 1958.]

[22] Longworth and Plesch, *Proc. Chem. Soc.*, 1958, 117.

716. *The Reactions of Organic Phosphates. Part I. The Hydrolysis of Methyl Dihydrogen Phosphate.*

By C. A. Bunton, D. R. Llewellyn, K. G. Oldham, and C. A. Vernon.

The hydrolysis of methyl dihydrogen phosphate has been investigated, by kinetic and isotope techniques, over the range of acidities pH 7 to 10M-perchloric acid. Four hydrolytic reactions have been identified. These involve the decomposition of (*a*) the monoanion with phosphorus–oxygen bond fission, (*b*) the neutral species with carbon–oxygen bond fission, and (*c*) the conjugate acid with both carbon–oxygen and phosphorus–oxygen bond fission. An oxygen exchange between methyl dihydrogen phosphate and solvent in strong acid solution has also been found. The mechanisms of all the reactions are discussed.

Nomenclature.—Throughout this and subsequent papers we describe accurately substances used in experimental work, *e.g.*, methyl disodium phosphate; names such as monomethyl phosphate, dimethyl phosphate, α-D-glucose 1-phosphate, etc., are used as collective designations for the various species, ionic and/or non-ionic, present in solution.

The mechanisms of the reactions of phosphate esters, although of interest to both chemists and biochemists, have not, until recent years, been systematically investigated. In this series of papers we propose to give an account, in mechanistic terms, of nucleophilic displacement processes, and especially those involving hydrolysis, as they occur in a group of relatively simple organic esters, of orthophosphoric acid. This may serve as a starting point for the study of the mechanisms of those more complex reactions, such as phosphate transfer, which are of direct interest to biochemists. Preliminary accounts of some of our work have already been published.[1,2]

The hydrolysis of organic phosphates is complicated by several factors. First, there is the problem of determining which of the possible forms of the substrate is the reactive species under specified conditions. For example, a phosphate monoester could undergo reaction as a dianion, a monoanion, a neutral molecule, or one of the conjugate acids. As will be seen, identification of the true factor can usually be made from the pH–rate profile and the dissociation constants of the substrate. Secondly, for each species reaction may occur with carbon–oxygen or with phosphorus–oxygen bond fission. Distinction between these two possibilities is conveniently made by using the isotope ^{18}O as a tracer, although, as will be seen below, complications may arise owing to concomitant exchange occurring in reactants and products. Thirdly, most of the reactions involve water (as distinct from hydroxide ions) as nucleophilic reagent and consequently the molecularity cannot be determined by the use of a simple-order criterion. In these cases, molecularity can be assigned with fair certainty only for reactions which are acid-catalysed and where the Zucker–Hammett criterion is applicable.

The essential features of the pH–rate profile for simple monoalkyl phosphates have been known for some time. Typically the rate of hydrolysis is very small in alkaline solution,[3,4] increases to a maximum at about pH 4, then falls to a minimum at about pH 0·5 and rises again in strongly acid solutions.[5,6,7] The French workers, Bailly [5] and Desjobert,[7] who largely pioneered this field, suggested that the maximum rate at about pH 4 was due to reaction of the monoanion, by some especially readily occurring mechanism.

[1] Barnard, Bunton, Llewellyn, Oldham, Silver, and Vernon, *Chem. and Ind.*, 1955, 760.
[2] Vernon, *Chem. Soc. Special Publ.*, No. 8, 1957, 17.
[3] Cavalier, *Compt. rend.*, 1898, **127**, 60.
[4] Plimmer and Scott, *J.*, 1908, **93**, 1699.
[5] Bailly, *Bull. Soc. chim. France*, 1942, **9**, 340, 405.
[6] Fleury, *Compt. rend.*, 1945, **221**, 416.
[7] Desjobert, *Bull. Soc. chim. France*, 1947, 809; *Compt. rend.*, 1947, **224**, 575; *Bull. Soc. Chim. biol.*, 1954, **36**, 475.

This view has recently been supported by the detailed investigations of Westheimer and his collaborators.[8,9] They found, for example, that the hydrolysis of optically active mono-2-methoxy-1-methylethyl phosphate had a maximum rate at pH 4 where the monoanion was the bulk component and that, under these conditions, hydrolysis proceeded with complete retention of configuration, indicating phosphorus–oxygen bond fission. Consistently, isotopically normal alcohol was recovered from a reaction run in water enriched with the isotope ^{18}O. It was suggested that reaction of the monoanion proceeded through some intermediate in which monoanion and water were linked by hydrogen bonds, the special reactivity of the monoanionic species of phosphate monoesters, compared with the corresponding neutral or dianionic species or with the monoanions of phosphate diesters, being due to its special ability to form such a complex. In the strongly acid region, mono-2-methoxy-1-methylethyl phosphate was found to undergo acid-catalysed hydrolysis, and the occurrence of carbon–oxygen bond fission was inferred from the fact that the alcohol recovered from the products was, under these conditions, considerably racemised.

In the present paper an investigation, by kinetic and isotope techniques, of the hydrolysis of monomethyl phosphate is reported. The results make possible an analysis of the mechanisms of hydrolysis more complete than any hitherto reported for a phosphate ester.

Experimental

Methyl dihydrogen phosphate was prepared by treatment of trisodium phosphate with dimethyl sulphate.[10] It was isolated as the barium salt (Found: Ba, 55·5. Calc. for CH_3O_4PBa: Ba, 55·5%). This was converted into the disodium salt which was used throughout the investigation. Its equivalent weight and water of crystallisation content were determined by titration and drying to constant weight respectively (Found: equiv., 263·3; H_2O, 41·2. Calc. for $CH_3O_4PNa_2,6H_2O$: equiv., 263·9; H_2O, 40·9%). Conventional tests for phosphate, sulphate, and barium ions gave negative results.

Determination of Dissociation Constants.—The values of the dissociation constants at 100° (the temperature of most of the kinetic runs) are required. It is clearly difficult to obtain accurate values at such a relatively high temperature: the following procedures, which yield approximate values, were therefore adopted:

(*a*) The second dissociation constant (pK_2) was determined from measurements of pH, by means of a standardised glass-electrode system, made in the course of titration of a solution of methyl disodium phosphate of known strength with standard 0·1M-hydrochloric acid. Let q and q' be the number of c.c. of acid added at equivalence (one sodium atom) and at any other point before equivalence, respectively. Then q' and $(q - q')$ are proportional to the concentrations of $MeHPO_4^-$ and $MePO_4^{2-}$ respectively. Activity effects being ignored, pK_2 is given by the Henderson equation:[11] $pK_2 = pH + \log [q'/(q - q')]$. At 1·05°, 11·0°, 22·5°, 34·2°, 58·0°, and 74·5°, the following values for pK_2 were obtained: 6·75, 6·61, 6·58, 6·59, 6·70, 6·71. The plot of pK_2 against temperature is roughly parabolic and simple extrapolation gave the value $pK_2 = 6·85$ at 100°. Harned and Embree[12] have pointed out that the variation of dissociation constant of weak acids with temperature can be reasonably well represented by the equation:

$$pK_T = pK_M + 5·0 \times 10^{-5}(T - \theta)^2$$

where K_M is the maximum value of the dissociation constant K_T and θ is the corresponding temperature. Application of this equation ($pK_M = 6·58$, $\theta = 26·0°$) gave the value $pK_2 = 6·85$ at 100°.

(*b*) The first dissociation constant (pK_1) was also determined from pH measurements. To a solution of the disodium salt enough standard hydrochloric acid solution was added to ensure

[8] Butcher and Westheimer, *J. Amer. Chem. Soc.*, 1955, **77**, 2420.
[9] Kumamoto and Westheimer, *ibid.*, p. 2515.
[10] Bailly, *Compt. rend.*, 1920, **170**, 1061.
[11] Glasstone, "Introduction to Electrochemistry," D. van Nostrand and Co. Inc., New York, 1942, p. 390.
[12] Harned and Embree, *J. Amer. Chem. Soc.*, 1934, **56**, 1050.

that the phosphate existed as a mixture of $MeHPO_4^-$ (salt) and MeH_2PO_4 (acid). The pH of this solution is approximately related to pK_1 by the equation

$$pK_1 = pH + \log [(C_{salt} + C_{H^+})/(C_{acid} - C_{H^+})]$$

where the concentrations C_{salt} and C_{acid} are derived from the initial concentration of methyl disodium phosphate and the amount of hydrochloric acid added, and C_{H^+} is calculated from the pH. The procedure is less precise than that for the determination of pK_2. At 22·0°, 35·0°, 58·0°, 60·0°, and 72·0°, the following values for pK_1 were obtained: 1·52, 1·45, 1·46, 1·43, 1·60. Simple graphical extrapolation gave the value $pK_1 = 1·61$ at 100°. Use of the Harned–Embree equation ($pK_M = 1·44$, $\theta = 42·0°$) gave the value $pK_1 = 1·65$.

Buffer Solutions.—The buffer solutions used for the kinetic experiments were those for which pH values have been given at 20° and 150° by Stene.[13] The values of the pH at intermediate temperatures were found by simple interpolation, and are given, together with the composition of the buffers, in Table 1.

Colorimetric Analysis of Phosphate Ions.—This was carried out by Allen's modified method,[14] with a Hilger " Spekker " Photoelectric Absorptiometer fitted with a red filter (Kodak 608). In mixtures containing perchloric acid, the amount of acid present in the aliquot part taken for analysis was allowed for when adding the perchloric acid necessary to develop the blue colour. This is necessary since the final intensity of colour developed is diminished by the presence of excess of perchloric acid.

The method of analysis was found to be insensitive to the presence of extraneous impurities with the exception of silicate. To prevent interference due to silicate the kinetic experiments were carried out in steamed-out Monax test-tubes.

Kinetic Experiments.—The following experimental details of a run at 100·1° and with $1·332 \times 10^{-3}$M-methyl disodium phosphate and 1·00M-perchloric acid are typical:

Aliquot parts (6 c.c.) of mixture were sealed in glass tubes, placed in the thermostat until thermal equilibrium was reached, removed at appropriate intervals, and cooled. Before analysis the tubes were allowed to reach a temperature of 20°. Aliquot parts (5 c.c.) were removed from each tube and the inorganic phosphate was determined colorimetrically. Since all the reactions were of first-order and since the intensity of colour developed in the phosphate determination was found to obey Beer's law, first-order rate coefficients (k_0) were calculated from the formula: $k_0 = (2·303/t) \log [(D_\infty - D_0)/(D_\infty - D_t)]$, where D_0, D_t, and D_∞ are the optical densities of the coloured solutions, obtained in the determination of phosphate, derived from aliquot parts taken at zero-time, time t, and complete reaction respectively. The results were:

Time (min.)	0	180	445	840	1440	2070	2795	3690	5130	∞
D	0·006	0·052	0·116	0·198	0·311	0·402	0·492	0·574	0·681	0·858
$10^4 k_0$ (sec.$^{-1}$)	—	5·15	5·20	5·07	5·13	5·03	5·05	4·93	5·12	—

The value, D_∞, was calculated from the known initial concentration of methyl disodium phosphate. In other experiments it was shown that the theoretical and the experimental infinity readings agreed within experimental error.

Table 1 gives the kinetic results obtained in the region pH 0—7·5. It can be seen that, in the region of pH 4, at the rate maximum, increase in buffer strength by some 50% or increase in total ionic strength is without appreciable effect on the rate. Similarly, change of solvent to deuterium oxide is, in so far as the water pH-scale is approximately applicable, also without effect. Arrhenius parameters for the reaction in the region of pH 4 were calculated by the method of least squares, from data at different temperatures, as $E = 30·6 \pm 0·2$ kcal. mole^{-1}, $A = 6·47 \times 10^{13}$ sec.$^{-1}$. Table 2 gives the results of kinetic runs carried out in strongly acidic solutions at 100·1°. The concentrations refer to room temperature.

Isotope Experiments.—A. *Isolation and isotopic analyses of products.* The hydrolysis of monomethyl phosphate was carried out, under a variety of conditions, in water containing an excess abundance of the isotope ^{18}O. Isotopic analyses of the products, *i.e.*, methanol and inorganic phosphate, were then made. The techniques were as follows:

(*a*) Methanol. The reaction mixture, usually about 250 c.c. and containing enough monomethyl phosphate to yield approximately 4 c.c. of methanol at complete reaction, was sealed in a

[13] Stene, *Rec. Trav. chim.*, 1930, **49**, 1133.
[14] Allen, *Biochem. J.*, 1940, **34**, 858.

glass ampoule and immersed in a thermostat until about 50% reaction had occurred. The ampoule was then cooled and opened. The contents were, where necessary, neutralised with solid potassium hydroxide and distilled, the first 20 c.c. of distillate being collected. This contained about 2 c.c. of methanol and was carefully fractionated through a small vacuum-jacketed column containing a metal spiral and having a low hold-up. Several samples of methanol were collected and the two middle samples (S_1 and S_2) were used for isotopic analysis. The remaining

TABLE 1. *Rates of hydrolysis of monomethyl phosphate at* pH 0—7·5 (100·1° *unless specified*).

pH	10^6k_0 (sec.$^{-1}$)	Composition *	pH	10^6k_0 (sec.$^{-1}$)	Composition *
0·02	5·09	1·0M-$HClO_4$	6·43	5·17	0·05M-P, 0·0455M-NaOH
0·32	3·85	0·5M-$HClO_4$	7·46	1·33	0·05M-H_3BO_3, 0·00261M-NaOH,
0·72	3·25	0·2M-$HClO_4$	—		0·05M-KCl
1·02	3·45	0·1M-$HClO_4$	4·08	8·27	0·075M-P
1·24	3·52	0·0645M-HCl, 0·05M-KCl	3·67	8·67	0·05M-P, 0·95M-$NaClO_4$
1·61	4·60	0·0263M-HCl, 0·05M-KCl	(4·17)	9·49 †	0·05M-P
2·20	6·72	0·0067M-HCl, 0·05M-KCl	4·12 [1]	0·815	0·05M-P
2·50	6·99	0·05M-P, 0·0396M-HCl	4·14 [2]	2·29	0·05M-P
4·17	8·23	0·05M-P	4·19 [3]	23·9	0·05M-P
5·60	7·38	0·05M-P, 0·030M-NaOH	4·21 [4]	50·0	0·05M-P

* P = potassium hydrogen phthalate. † In 95% deuterium oxide at 101·0°.
[1, 2, 3, 4] At 80·0, 89·0, 109·7, and 117·2° respectively.

TABLE 2. *Hydrolysis of monomethyl phosphate in strongly acidic solutions* (100·1°).

M-$HClO_4$	10^6k_0 (sec.$^{-1}$)	M-$HClO_4$	M-$NaClO_4$	10^6k_0 (sec.$^{-1}$)	M-$HClO_4$	M-$NaClO_4$	10^6k_0 (sec.$^{-1}$
1·00	5·08	2·00 [1]	6·00	20·8	6·00 [2]	1·00	26·8
2·00	7·77	4·00 [1]	4·00	26·7	1·50 [3]	2·50	7·53
3·00	11·3	6·00 [1]	2·00	33·0	2·50 [3]	1·50	10·3
4·00 [3]	15·0	7·00 [1]	1·00	35·3	3·00 [3]	1·00	11·6
4·00 *	15·2	2·00 [2]	5·00	15·4	3·50 [3]	0·50	12·5
5·00	18·5	4·00 [2]	3·00	21·8			
6·00	24·2						
7·00 [2]	31·5						
8·00 [1]	41·5						
9·00	54·7						
10·00	78·5						

[1, 2, 3] Solutions of total ionic strength (μ) 8·00, 7·00, and 4·00M respectively.
* In 67·6% deuterium oxide.

samples were mixed with isotopically normal water and refractionated, two middle samples (S_3 and S_4) again being analysed. Comparison of the results from the two pairs of samples provides a check on the efficiency of the distillation. The methanol samples were pyrolysed *in vacuo* to carbon monoxide over carbon heated by a radio-frequency heater. The carbon monoxide was analysed mass-spectrometrically. The following details are typical: a solution of methyl disodium phosphate (17·2 g. in 250 c.c.) in 5M-perchloric acid was heated for 9 hr. at 100·1°. The solvent contained 1·87 atom % excess abundance * of ^{18}O. The analysis of carbon monoxide obtained from the methanol isolated from the reaction gave S_1 1·40, S_2 1·47, S_3 1·41, S_4 1·52 atom % of ^{18}O.

(*b*) Inorganic phosphate. A modification of the method originally given by Cohn was used.[15] The solution remaining after the distillation of methanol, as described above, was centrifuged, if necessary, to remove potassium perchlorate and adjusted to *ca.* pH 10. Sufficient barium chloride solution was added to precipitate all the inorganic phosphate as barium phosphate [$Ba_3(PO_4)_2$]. The precipitate was centrifuged off and washed several times with ice-cold water (in which methyl barium phosphate is relatively soluble). The barium phosphate was then dissolved in the minimum amount of 2M-hydrochloric acid and reprecipitated by adding 2M-sodium hydroxide until the pH was *ca.* 10. The precipitate was removed by centrifugation and washed with cold water. This procedure was repeated four times to ensure complete removal of adsorbed impurities. The barium phosphate was again dissolved in the minimum amount of 2M-hydrochloric acid, and a solution of potassium sulphate added dropwise until no more

* Subsequent figures also refer to atom % excess over the normal abundance.

[15] Cohn, *J. Biol. Chem.*, 1949, **180**, 771.

barium sulphate was precipitated. (It is important to avoid excess of potassium sulphate.) The barium sulphate was removed by centrifugation and the supernatant liquid adjusted to pH 4·5 with potassium hydroxide solution. Two volumes of ethanol were then added and the precipitated potassium dihydrogen phosphate was centrifuged off, washed with ethanol and then with ether, and dried at 100° for 2 hr. Samples (*ca.* 0·3 g.) were then sealed in glass tubes (vol. *ca.* 5 c.c.) with carbon dioxide at *ca.* 8 cm. pressure, and were heated at 200° for 24 hr.* The carbon dioxide was then analysed mass-spectrometrically. A typical result is that obtained from the experiment described in the last section: the ^{18}O contents of the carbon dioxide from two samples were 0·278 and 0·280 atom % of ^{18}O.

B. *Calculation of the position of bond fission.* It being assumed that no exchange reactions involve the oxygen atoms of the solvent and of the factors and products, then if N_S, N_M, and N_P are the excess abundance of ^{18}O in the solvent, methanol, and inorganic phosphate respectively, the percentage of the total reaction proceeding by a process involving carbon–oxygen bond fission is $100 \times N_M/N_S$, and the corresponding function giving the percentage of phosphorus–oxygen bond fission $100 \times 4N_P/N_S$.† Further, the two percentages, which are obtained independently, should, for hydrolysis under specified conditions, total 100, within experimental error.

However, methanol, in aqueous acid, undergoes oxygen exchange with the solvent,[16] and phosphate ions undergo a similar exchange both in acidic solution and in the range pH 0—7.[17] Consequently, except for the case of methanol isolated from reactions run in neutral or slightly acidic conditions, the above simple way of dealing with the isotopic data is inapplicable.

The proportion of carbon–oxygen bond fission, Q_O, can be calculated from the isotopic enrichment, N_M, of the isolated methanol, and of the solvent N_S, by the following equation which takes account of the exchange reaction between methanol (M) and the solvent:

$$Q_O = \frac{(N_M R/N_S - 1)(k_0 - k_E^M) - (k_E^M \exp - k_0 t) + (k_0 \exp - k_E^M t)}{k_0 (\exp - k_E^M t - \exp - k_0 t)}$$

where R is the fraction of monomethyl phosphate which has undergone hydrolysis in time t and k_E^M is the first-order rate coefficient for the oxygen exchange of methanol under the reaction conditions.

The proportion of phosphorus–oxygen bond fission, Q_P, can be calculated from the isotopic enrichment, N_P, of the isolated inorganic phosphate by a similar equation:

$$Q_P = \frac{4[N_P R/N_S - 1)(k_0 - k_E^P) - (k_E^P \exp - k_0 t) + (k_0 \exp - k_E^P t)]}{k_0 (\exp - k_E^P t - \exp - k_0 t)}$$

where k_E^P is the first-order rate coefficient for the oxygen exchange of inorganic phosphate (all four oxygen atoms) under the reaction conditions. The derivation of these equations is given in the Appendix.

Table 3 gives the results obtained at 100·1°.

TABLE 3. *Isotope experiments.*

Conditions	Time (hr.)	$10^6 k_0$ (sec.$^{-1}$)	$10^6 k_E^M$ (sec.$^{-1}$)	$10^6 k_E^P$ (sec.$^{-1}$)	N_S	N_M	N_P	Q_O	Q_P
5M-$HClO_4$	9	18·5	7·58 [18]	2·50 [17]	1·87	1·45	0·279	73	44·5
pH 4·0	48	8·23	—	0·92 [17]	0·78	0·015	0·26	1·9	107
pH 6·5	175	5·17	—	—	0·97	0·01	—	1·0	—
ca. pH 1, 9M-$NaClO_4$...	16	—	—	—	0·60	0·50	—	84·0	—

(C) *Isotopic analysis of substrate.* It will be seen from Table 3 that, for hydrolysis in strongly acid solution, the sum of the percentages of reaction proceeding by phosphorus–oxygen and carbon–oxygen bond fission significantly exceeds 100. This discrepancy must mean that some

* Isotopic fractionation in the dehydration of the phosphate has been ignored.

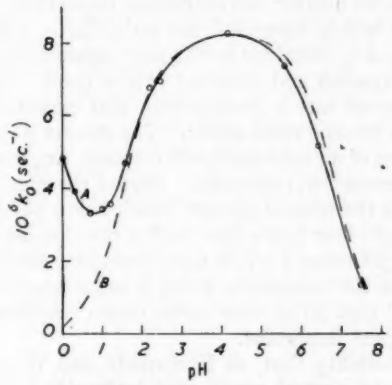
† The factor four arises because, whereas hydrolysis can isotopically enrich only one of the four oxygen atoms of the phosphate, all four contribute to the isotope content of the water obtained by heating the potassium dihydrogen phosphate. Analysis of the carbon dioxide after equilibration with this water effectively gives the average isotopic enrichment of all the oxygen atoms of the inorganic phosphate.

[16] Oldham, unpublished experiments.
[17] Welch, unpublished experiments.

process exists whereby the substrate can become isotopically enriched. The following experiment was designed to measure the extent of this enrichment. A solution of methyl disodium phosphate (17 g. in 250 c.c. of 5M-perchloric acid) was allowed to hydrolyse for 9 hr. at 100·1°; the solvent contained 1·87 atom % of ^{18}O. Inorganic phosphate was then removed as already described. To the remaining solution enough barium chloride was added to convert the monomethyl phosphate into its barium salt. The mixture was set aside and then centrifuged. The supernatant liquid was heated to the b. p. and the precipitated methyl barium phosphate filtered off. The precipitate was washed several times with hot water and finally with acetone. Colorimetric analysis showed it to contain less than 1% of inorganic phosphate. It was then necessary to hydrolyse the isolated monomethyl phosphate under conditions in which no exchange of either organic or inorganic phosphate would occur. The following two procedures were used:

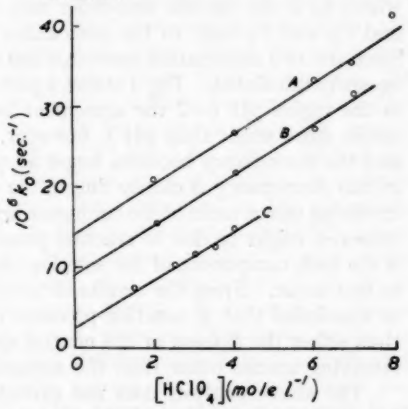
(*a*) The barium salt (1·9 g.) was dissolved in the minimum quantity of 2M-hydrochloric acid, and the barium was removed by quantitative precipitation with potassium sulphate solution. The remaining solution was mixed with three volumes of 4M-hydriodic acid and heated for 20 min. at 100°. Inorganic phosphate was then isolated and analysed as described before, giving

FIG. 1. *Hydrolysis of monomethyl phosphate at 100·1°.*



A, Experimental. B, Calculated.

FIG. 2. *Acid-catalysed hydrolysis of monomethyl phosphate at constant ionic strength at 100·1°.*



A, $\mu = 8·0$, gradient $= 3·10 \times 10^{-6}$. *B*, $\mu = 7·0$, gradient $= 3·12 \times 10^{-6}$. *C*, $\mu = 4·0$, gradient $= 3·02 \times 10^{-6}$.

N_P 0·075, 0·050% of ^{18}O. The procedure is satisfactory because iodide ion enormously speeds the hydrolysis of monomethyl phosphate,[16] but does not catalyse the exchange reaction of inorganic phosphate.[17]

(*b*) The barium salt (1·8 g.) was converted into the potassium salt as described above. To the resulting solution were added 200 c.c. of acetate buffer (0·20M; pH 5·0) and 10 c.c. of a concentrated solution of human prostatic acid phosphatase. The mixture was kept for 20 hr. at 20°, after which the inorganic phosphate which had been formed was isolated and analysed, giving N_P 0·065 atom % of ^{18}O. The validity of this procedure depends on the fact that exchange between phosphate and the solvent does not occur under the specified conditions.[18]

One possible explanation for the isotopic enrichment observed in the substrate is that it arises from the reverse reaction, *i.e.*, from formation of monomethyl phosphate from the hydrolysis products. To test this possibility a solution containing inorganic phosphate and methanol (0·5M) in 5M-perchloric acid which had been heated at 100° for a prolonged period was analysed and found to contain more than 98% of the original inorganic phosphate. A simple calculation now eliminates the possibility. The equilibrium constant, $[MeH_2PO_4]/[MeOH][H_3PO_4]$ is, from the analytical figure, less than 0·04; hence the second-order rate coefficient for the

[18] Bunton, Silver, and Vernon, *Proc. Chem. Soc.*, 1957, 348.

hypothetical reaction between phosphate and methanol would be less than $7{\cdot}3 \times 10^{-7}$ l. mole^{-1} sec.$^{-1}$. Under the conditions of the partial hydrolysis experiment this means that less than 2% of the monomethyl phosphate isolated could have been formed by recombination of products and this could not account for the observed enrichment.

Discussion

(a) *Hydrolysis of the Monoanion.*—The variation of rate of hydrolysis with pH in the region pH 1—7 is, as other workers have pointed out,[5,7-9] paralleled by the variation in concentration of the monoanion species. From the dissociation constants, simple calculation shows that, at pH 4·17, 99·9% of the monomethyl phosphate is present as the monoanion. The first-order rate coefficient (k_0) at any other pH is, therefore, if the monoanion is the only reactive species, given by:

$$k_0 = k_M C_M / C_P \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where k_M is the specific first-order rate coefficient, $8{\cdot}23 \times 10^{-6}$ sec.$^{-1}$, for the monoanion and C_M and C_P refer to the monoanion and stoicheiometric concentrations respectively. Since the two dissociation constants are relatively widely separated, the ratio, C_M/C_P, can be easily calculated. Fig. 1 shows a plot of values of k_0 (obtained in this way), against pH: in the region pH 1—7 the agreement between expected and observed rate is good. In media more acidic than pH 1, however, the observed rate is greater than that expected and the discrepancy becomes larger as the media become more acidic. The greater part of this discrepancy is clearly due to the emergence of an acid-catalysed reaction, *i.e.*, one involving one or more of the conjugate acids of monomethyl phosphate. Part of the effect, however, might be due to reaction proceeding *via* the neutral species, which below pH 1 is the bulk component of the solution, and we shall show below that such a reaction does in fact occur. From the results obtained in the pH range 1—7, it may, therefore, safely be concluded that (i) reaction proceeds mainly *via* the monoanion which is more reactive than either the dianion or the neutral species and that (ii) in more acidic media reactions involving species other than the monoanion become important.

The above analysis does not exclude the possibility that, as Kumamoto and Westheimer have pointed out,[9] the true factors are the neutral species and hydroxide ions, since such a reaction would have the same kinetic form as that involving the monoanion and a water molecule. In this case the specific rate coefficient for this hypothetical reaction would be

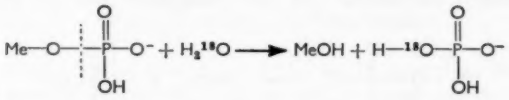
$$k_M \,.\, C_P / (C_{OH^-} \,.\, C_N) = ca.\ 10^7 \text{ l. mole}^{-1} \text{ sec.}^{-1}$$

where C_N and C_{OH^-} are the concentrations of neutral species and hydroxide ions respectively at pH 4·17. This value should be compared with the value $3{\cdot}3 \times 10^{-2}$ l. mole^{-1} sec.$^{-1}$ for the known second-order reaction between trimethyl phosphate and hydroxide ions[19] at 100°. Such a large rate difference would be inexplicable and the view that the reaction is between the neutral species and hydroxide ions is, therefore, to be rejected.

The isotope experiments (Table 3) show that hydrolysis of the monoanion proceeds with phosphorus–oxygen bond fission. The value of Q_P (percentage of phosphorus–oxygen bond fission) actually obtained (107%) shows that there was, in fact, rather more tracer in the inorganic phosphate product than could be accounted for by simple hydrolysis involving phosphorus–oxygen bond fission. (In calculating Q_P the exchange reaction of inorganic phosphate has already been allowed for.) The discrepancy, however, is probably just within the experimental uncertainties of the phosphate analysis and it is

[19] Barnard, unpublished experiments.

not considered that it is indicative of a concomitant exchange involving monomethyl phosphate. The reaction may, therefore, be formulated:



Hydrolysis of monoanion species with phosphorus–oxygen bond fission has now been demonstrated in several cases, *viz.*, α-D-glucose-1 (following paper), phenyl,[20] *p*-tolyl,[20] *p*-nitrophenyl,[20] glycerol-1,[21] glycerol-2,[21] 2-methoxy-1-methylethyl,[8] and benzyl[9] phosphate monoesters. The reaction is probably a general one and it can be expected that it will be observed with any monosubstituted phosphate, in solutions of *ca.* pH 4, unless it is obscured by some especially ready reaction involving the neutral species and proceeding with carbon–oxygen bond fission.

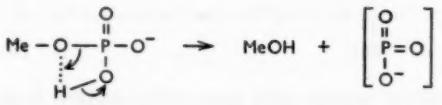
It is difficult to specify the precise mechanism by which the monoanion of an orthophosphate monoester undergoes hydrolysis largely because, for the conditions under which reaction occurs, there is no appropriate experimental criterion of molecularity. Certain features of the mechanism can, however, be inferred from the available data, and and proposed mechanistic scheme must be consistent with these. First, the reaction is limited to those species containing an ionised and an un-ionised acidic group, *i.e.*, the groups OH and O^- must be present. This emerges from the following comparisons. The corresponding reaction for dimethyl phosphate, as will be shown in Part III, cannot have a first-order rate coefficient greater than $1{\cdot}6 \times 10^{-9}$ sec.$^{-1}$ (at 100°). Hence the rate factor between monomethyl and dimethyl phosphate for this reaction is at least 5000, and may, since the reaction has not actually been observed in the phosphate diester, be very much larger than this (cf. ref. 9). Similarly, the dianion $MePO_4^{2-}$, which like the monoanion $Me_2PO_4^-$, contains no hydroxyl group, is very resistant to hydrolysis. The neutral species MeH_2PO_4, as will be shown later, does undergo hydrolysis (k_N = *ca.* 5×10^{-7} sec.$^{-1}$ at 100·1°) but with carbon–oxygen fission. If we assume that a reaction involving phosphorus–oxygen bond fission and, therefore, analogous to the reaction of the monoanion, would not be experimentally distinguished if its rate coefficient were less than a tenth of the total for the neutral species, then an upper limit (*ca.* 5×10^{-8} sec.$^{-1}$) can be set for its rate coefficient. This means that the monoanion is at least a hundred times more reactive, and the true rate factor may be very much larger. Secondly, the summarised data [2] for a variety of compounds of the general formula, RO·PO(O^-)OH, where R is alkyl, aryl, or pyranosyl, show that the rates of hydrolysis and the Arrhenius parameters are not very sensitive to the nature of R. Although there tends to be a correlation between rate of hydrolysis and stability of the anion RO^-, the spread in the values of the kinetic parameters is small. This might be taken as support for the view that the rate-determining step does not involve separation of the anion RO^-. Thirdly, as can be seen from Table 1, the reaction of monomethyl phosphate, and no doubt, by analogy, of other phosphate monoester monoanions, is not catalysed by general acids and is little influenced by large increases in ionic strength.

Three mechanisms are consistent with the observed facts, namely: (*a*) The negative charge on the O^- group is imagined as the " driving-force " of the reaction. At the same time hydrogen migration from the hydroxyl group to the ester-oxygen atom occurs (cf. refs. 8 and 9). The immediate products are methanol and the hypothetical metaphosphate ion. The latter has been postulated as an intermediate in some phosphorylations [22] and would presumably undergo rapid hydration to orthophosphoric acid.[23]

[20] Silver, unpublished experiments.
[21] Swoboda and Crook, *Biochem. J.*, 1955, **59**, xxiv.
[22] Todd, Arthur D. Little Lectures, Massachusetts Inst. Technology, 1954.
[23] Topley, *Quart. Rev.*, 1949, **3**, 345.

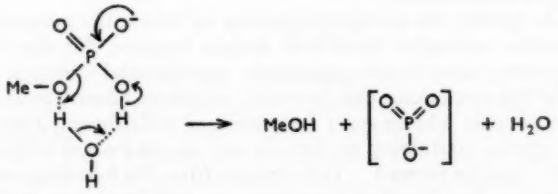
(*b*) A mechanism involving bimolecular attack on the phosphorus with simultaneous hydrogen migration to the ester-oxygen atom in the rate-determining step is also acceptable, and has been discussed elsewhere.[2] (*c*) The suggestion due to Westheimer and his

(*a*)



colleagues [8,9] that the reaction involves a cyclic intermediate formed by hydrogen-bonding between the monoanion and a water molecule is attractive and has recently been used as a basis for a model of the reaction when catalysed by the enzyme, prostatic acid phosphatase.[18] Each of these mechanisms involves (i) the monoanion specifically, (ii)

(*c*)



phosphorus–oxygen bond fission, and (iii) hydrogen-transfer (either from the hydroxyl group of the phosphate or from a water molecule to the ester-oxygen atom). Distinction between them must await further relevant information.

(b) *Hydrolysis of the Neutral Species.*—In solutions containing M-perchloric acid the predicted first-order rate coefficient for a reaction proceeding entirely through the monoanion is $0{\cdot}183 \times 10^{-6}$ sec.$^{-1}$ (from equation 1). The observed rate is $5{\cdot}08 \times 10^{-6}$ sec.$^{-1}$ and hence for solutions of stoicheiometric acidity greater than M, the contribution from hydrolysis of the monoanion is negligible. There remains, however, the possibility that in strongly acidic solutions hydrolysis proceeds partly through the neutral species which is, under these conditions, the bulk component. That this is the case can be seen from Fig. 2 in which experimentally obtained first-order rate coefficients (k_0) are plotted against stoicheiometric acidity (C_{H^+}) for a series of constant ionic strengths, $\mu = (NaClO_4 + HClO_4)$. For each ionic strength the plot of k_0 against C_{H^+} is a straight line, the slope and the intercept (at $C_{H^+} = 0$) of which measure, for a particular ionic strength, the rate coefficients for the reactions of the conjugate acid and of the neutral species respectively. Since each line has, within the experimental scatter, the same slope, corresponding to a specific rate coefficient k_A of $3{\cdot}08 \times 10^{-6}$ l. mole^{-1} sec.$^{-1}$, the acid-catalysed reaction is, clearly, not subject to a large salt effect. The rate coefficient for the reaction of the neutral species, however, as measured by the intercepts in Fig. 2, increases as μ increases; this reaction, therefore, exhibits a large positive salt effect.

It has been suggested [24] that, for reactions in not very dilute solutions involving uncharged reagents, the dependence of rate coefficient on ionic strength has the form:

$$k_N = k_N^0 \exp b\mu \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where k_N and k_N^0 are the specific rate coefficients at ionic strengths μ and zero respectively, and b is a constant. The hydrolysis of the neutral species obeys this equation since a straight line is obtained by plotting values of log k_N (calculated from the intercepts of Fig. 2) against μ. From the slope and intercept of the line b and k_N^0 are found to be

[24] Long and McDevit, *Chem. Rev.*, 1952, **51**, 119.

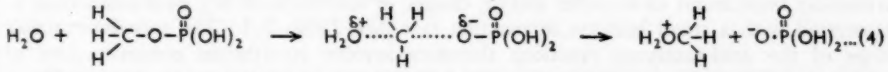
0·423 and 0·50 × 10^{-6} sec.$^{-1}$ respectively. Hence the first-order rate coefficient (k_N') for hydrolysis due to the neutral species under any particular condition is:

$$k_N' = \frac{C_N}{C_P} \cdot 0{\cdot}50 \times 10^{-6} \exp 0{\cdot}423\mu \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where C_N/C_P is the proportion of monomethyl phosphate present as the neutral species.

The position of bond fission for the neutral species is not easy to determine since, in dilute solutions, there is no part of the pH–rate profile where its hydrolysis is predominant. For example, at pH 1, where the neutral species is the bulk component (*ca.* 80%), the rate coefficient for its hydrolysis is, as predicted by equation 3, *ca.* 0·40 × 10^{-6} sec.$^{-1}$, whereas the observed rate coefficient is 3·45 × 10^{-6} sec.$^{-1}$. In solutions containing 9M-sodium perchlorate, however, the rate coefficient for hydrolysis of the neutral species rises to *ca.* 1·3 × 10^{-5} sec.$^{-1}$, and under these conditions isotopic analysis should indicate, at least for the bulk of the reaction, the position of bond fission. Hydrolysis at *ca.* pH 1 in the presence of 9M-sodium perchlorate gave 84% of carbon–oxygen bond fission. Since, under these conditions, the reaction of the neutral species accounts for *ca.* 80% of the total rate and the remainder is mostly due to hydrolysis of the monoanion (phosphorus–oxygen bond fission) it may be concluded that hydrolysis of the neutral species proceeds predominantly with carbon–oxygen bond fission.

The molecularity of the reaction cannot be directly determined and two possible mechanisms must be considered. One involves the rate-determining formation of a methyl cation [S_N1(C)] and the other a bimolecular attack on carbon by a water molecule [S_N2(C)]. Since water is a relatively strong nucleophile towards a saturated carbon atom whereas the formation of a methyl cation is energetically difficult, the second mechanism is to be preferred and can be formulated as in equation (4).



(c) *Hydrolysis of the Conjugate Acid.**—It is possible, from equations (1) and (3), to calculate, for any particular acidity, the first-order rate coefficient for that proportion of the total reaction which proceeds *via* the monoanion and the neutral molecule. By subtraction from the experimentally observed value, the first-order rate coefficient (k_0') of the acid-catalysed hydrolysis (*i.e.*, that of the conjugate acid) can be found. Such calculations, made with results obtained from experiments in which no sodium perchlorate was added and given in Table 2, yield the values given in Table 4.

A plot of the first-order rate coefficients in Table 4 against acidity shows that, up to 7M-perchloric acid, k_0' increases in proportion with stoicheiometric acidity; in more acidic solutions, however, the rate of increase of k_0' is rather greater. The linear portion of the curve gives a value for the specific second-order rate coefficient for the acid-catalysed reaction (k_A) of 3·08 × 10^{-6} l. mole^{-1} sec.$^{-1}$, in close agreement with the value found from the experiments at constant ionic strengths (see section *b* above).

The experiments with ^{18}O showed that, in strongly acid solution, both carbon–oxygen and phosphorus–oxygen fission occur. Isotopic analysis of the methanol produced indicated that the proportion of the total reaction proceeding (in 5M-perchloric acid) by phosphorus–oxygen bond fission is 0·27. Similar analysis of the inorganic phosphate produced, however, gave a value, for the same quantity, of 0·44. This discrepancy is not due to experimental error and immediately suggests the occurrence of an exchange between monomethyl phosphate and solvent. This explanation was confirmed by showing that monomethyl phosphate, recovered from a partial hydrolysis, contained significant amounts of tracer. Whatever the mechanism of this exchange, the ester-oxygen cannot

* By conjugate acid is meant the sum of the possible structures obtained by adding a proton to uncharged monomethyl phosphate. The possible structures are differentiated only for purposes of detailed mechanistic discussion.

become isotopically enriched, and consequently isotopic analysis of the methanol, which can only contain the ester-oxygen atom or one derived from the solvent, must provide a true measure of the proportion in which the two possible types of bond fission occur. Hence, it may be concluded that, in 5M-perchloric acid, 27% of the molecules undergoing hydrolysis do so by phosphorus–oxygen bond fission.

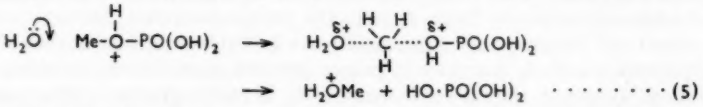
TABLE 4. *Rate coefficients for acid-catalysed hydrolysis of monomethyl phosphate after correction for hydrolysis of neutral molecule.*

$HClO_4$ (M)	$10^6k_0'$ (sec.$^{-1}$)	$10^6k_A = 10^6k_0'/C_{H^+}$ (l. mole^{-1} sec.$^{-1}$)	$HClO_4$ (M)	$10^6k_0'$ (sec.$^{-1}$)	$10^6k_A = 10^6k_0'/C_{H^+}$ (l. mole^{-1} sec.$^{-1}$)
1·0	4·12	4·12	6·0	17·7	2·93
2·0	6·48	3·23	7·0	21·7	3·10
3·0	9·42	3·13	8·0	26·4	3·30
4·0	12·2	3·05	9·0	31·8	3·53
5·0	14·3	2·85	10·0	43·3	4·33

Tables 2 and 4 shows that, whereas, in 5M-perchloric acid at 100·1°, the observed first-order rate coefficient is $18{\cdot}5 \times 10^{-6}$ sec.$^{-1}$, that due to the acid-catalysed reaction is $14{\cdot}3 \times 10^{-6}$ sec.$^{-1}$; the remainder of the reaction is due, as was shown in section (*b*), to hydrolysis of the neutral molecule. The latter process involves carbon–oxygen bond fission and hence the true proportion of phosphorus–oxygen bond fission for the acid-catalysed reaction must be greater than 0·27: simple calculation gives 0·35. The two processes which make up the acid-catalysed reaction, therefore, have specific second-order rate coefficients of $k_A(C) = 0{\cdot}65k_A$ and $k_A(P) = 0{\cdot}35k_A$ where the symbols in parentheses indicate the positions of bond fission.

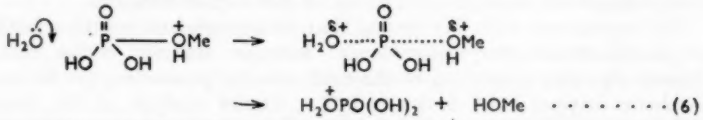
The formation of the conjugate acid involved in the acid-catalysed reaction is not rate-determining since (i) proton-transfers, in strongly acid solution, to an oxygen atom have invariably been found to be rapid and (ii) change of solvent to 67·6% deuterium oxide is associated with a small increase in reaction rate (see Table 2).* The rate-determining steps of the acid-catalysed reactions therefore involve equilibrium concentrations of conjugate acid, and, since proportionality between rate and stoicheiometric acidity is observed, both reactions should, on the Zucker–Hammett hypothesis, be bimolecular and involve a water molecule in their rate-determining steps.

The reaction which proceeds by carbon–oxygen bond fission may be formulated in conventional manner as a nucleophilic attack by a water molecule on the carbon atom of a monomethyl phosphate molecule containing a protonated ester-oxygen atom, *viz.*:



(5)

The reaction involving phosphorus–oxygen bond fission may be similarly formulated as a nucleophilic attack on the phosphorus atom, *viz.*:



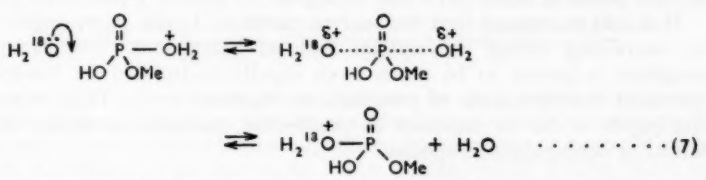
(6)

* It should be noted that the increase in rate would undoubtedly have been greater had the experiment been performed in 100% deuterium oxide since Wiberg [25] has shown that the effect of deuterium oxide on acid-catalysed rates increases more rapidly than does the mole fraction in the region of 100% deuterium oxide.

In the present case some 15% of the reaction involved bimolecular attack on the neutral species (*i.e.*, was not acid-catalysed) and since this reaction may well be slower in deuterium oxide,[26] the true increase for the acid-catalysed reaction may have been partially masked.

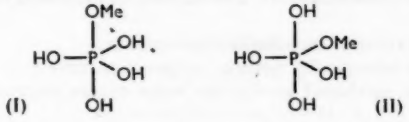
[25] Wiberg, *Chem. Rev.*, 1955, **55**, 713.
[26] Oldham, Ph.D. Thesis, London, 1957.

The exchange reaction, the molecularity of which has not been determined but which, by analogy, may be assumed to be bimolecular, is most simply formulated as involving an alternative conjugate acid (*i.e.*, one in which one of the hydroxyl groups is protonated), *viz.*:



The reactions (6) and (7) then involve displacement from the phosphorus atom of whichever attached group is protonated and their relative rates would depend partly on the relative concentrations of the two conjugate-acid forms.

Since phosphorus can use *d*-orbitals for covalent binding, nucleophilic displacement on phosphorus need not involve synchronous bond-making and bond-breaking. In alternative formulations we would suppose that the reactions proceed *via* a common intermediate containing five groups covalently bound to the phosphorus atom. Several structures, of which (I) and (II) are two, or their protonated forms may be written for such an intermediate. Hydrolysis or exchange will result if the intermediate, after protonation, loses respectively MeOH or H_2O. At the moment, however, no experimental test is available to distinguish between these possibilities.



(d) *General.*—Four hydrolytic mechanisms have been identified for monomethyl phosphate and their characteristics are summarised in Table 5.

TABLE 5. *Summary of reaction mechanisms for hydrolysis of monomethyl phosphate.*

Form	$10^6 \times$ Specific rate coefficient (100·1°)	Bond fission	Molecularity	Salt effect
(A) Monoanion	8·23 [a]	P–O	?	Nil
(B) Neutral species	0·50 [a,c]	C–O	2	Large +
(C) Conjugate acid	2·00 [b]	C–O	2	Nil
(D) Conjugate acid	1·08 [b]	P–O	2	Nil

[a] Sec.$^{-1}$. [b] l. mole^{-1} sec.$^{-1}$. [c] At $\mu = 0$.

The rate coefficient k_0 (sec.$^{-1}$) for hydrolysis at any acidity within the range pH 7·5 to 7M-perchloric acid is given by equation (8):

$$10^6 k_0 = \frac{C_M}{C_P} \cdot 8{\cdot}23 + \frac{C_N}{C_P} \cdot 0{\cdot}50 \,.\, \exp\,(0{\cdot}423\mu) + \frac{C_N}{C_P} \cdot 3{\cdot}08 C_{H^+} \quad . \quad . \quad . \quad (8)$$

and the percentage phosphorus–oxygen bond fission (Q_P) by:

$$Q_P = \frac{8{\cdot}23C_M + 1{\cdot}08C_{H^+}C_N}{8{\cdot}23C_M + 0{\cdot}50C_N \exp\,(0{\cdot}423\mu) + 308C_{H^+}C_N}$$

The fit of equation (8) is very good except in the region pH 1—0 where the uncertainties associated with the dissociation constants become relatively more important.

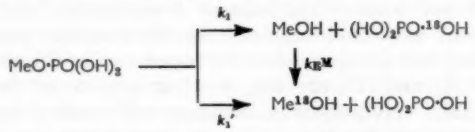
The behaviour of monomethyl phosphate may be taken as typical of that of primary monoalkyl phosphates. For groups other than methyl, reactions (B) and (C) will be relatively suppressed, especially if steric factors become important; the general character

of the rate profile will, however, remain the same. For compounds containing a tertiary alkyl group unimolecular reactions of the neutral species and conjugate acid involving carbon–oxygen bond fission will become relatively important and the minimum in the pH–rate profile at about pH 0 may disappear [cf. glucose 1-phosphate (following paper)].

It should be stressed that the analysis presented in this paper applies only to solutions not containing strong nucleophiles such as halide ions. For example, monomethyl phosphate is known to be much more rapidly hydrolysed by halogen acids than by equivalent concentrations of perchloric or sulphuric acid. This, as we shall show in a later paper, is due to incursion of bimolecular reactions involving halide ions and the neutral or conjugate acid species.

Appendix

(a) *Calculation of* Q_C.—Let k_1 be the first-order rate coefficient for hydrolysis of monomethyl phosphate with phosphorus–oxygen bond fission,



k_1' the first-order rate coefficient for its hydrolysis with carbon–oxygen bond fission,

k_E^M the first-order rate coefficient for the isotopic equilibrium between the oxygen atoms of water and methanol,*

a_0 the initial concentration of monomethyl phosphate,

b the concentration of isotopically normal methanol at time t,

c the concentration of methanol having the same excess abundance of ^{18}O as the solvent at time t,

N_S the excess abundance of ^{18}O in the solvent,

N_M the excess abundance of ^{18}O in the methanol isolated from the reaction mixture, *i.e.*, $N_M/N_S = c/(b + c)$.

The total rate of hydrolysis, k_0, is:

$$k_0 = k_1 + k_1' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

and

$$Q_C = k_1'/k_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

and $(b + c)/a_0 = R$, where R is the fraction of monomethyl phosphate hydrolysed at time t.

Therefore,

$$c/a_0 = N_M R/N_S \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Now

$$dc/dt = k_1'[a_0 - (b + c)] + k_E^M b \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

and, since the total reaction is of the first-order,

$$a_0 - (b + c) = a_0 \exp - k_0 t \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Eliminating b from (4) and (5) we have:

$$dc/dt + k_E^M c = k_E^M a_0 + a_0(k_1' - k_E^M) \exp - k_0 t \quad . \quad . \quad . \quad . \quad . \quad (6)$$

Integration after multiplication by $\exp k_0 t$ gives:

$$c \exp k_0 t = a_0 \exp k_0 t - a_0 \frac{(k_1' - k_E^M)}{(k_0 - k_E^M)} \exp [- (k_0 - k_E^M)t] + I$$

where I, since when $t = 0$, $c = 0$, is found as:

$$I = a_0 k/(k_0 - k_E^M)$$

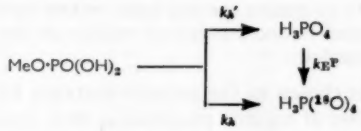
* In this particular case, because only one atom is exchanged and because the solvent is in large excess, k_E^M is also the first-order rate coefficient for the oxygen exchange irrespective of labelling.

Rearrangement after elimination of k_1 and k_1' by (1) and (2) gives:

$$\frac{c}{a_0} = \frac{N_M}{N_S} \cdot R = 1 - \frac{(Q_O k_0 - k_E^M) \exp - k_0 t + (1 - Q_O) k_0 \exp - k_E^M}{k_0 - k_E^M}$$

whence
$$Q_O = \frac{(N_M R/N_S - 1)(k_0 - k_E^M) - (k_E^M \exp - k_0 t) + (k_0 \exp - k_E^M t)}{k_0[(\exp - k_E^M t) - (\exp - k_0 t)]} \quad . \quad (7)$$

(b) *Calculation of* Q_P.—The derivation of the expression for Q_P is a little more complicated because, whereas hydrolysis with phosphorus–oxygen bond fission leads to inorganic phosphate with only one oxygen atom enriched isotopically, the oxygen exchange of inorganic phosphate leads to isotopic enrichment of all four atoms. It is mathematically simpler to set up the equations in terms of the hypothetical process:



in which hydrolysis of monomethyl phosphate produces either isotopically normal inorganic phosphate (first-order rate coefficient k_h') or inorganic phosphate with all four oxygen atoms having the same excess abundance of ^{18}O as the solvent. The first-order rate coefficient for the isotopic equilibration of inorganic phosphate is k_E^P.* The coefficients k_h' and k_h are related to those previously defined (on the assumption of random distribution of tracer in the phosphate) by:

$$k_h = k_1/4 \quad . \quad (8)$$

and
$$(k_h' - 3k_h) = k_1' \quad . \quad (9)$$

Now
$$Q_P = 4k_h/(k_h + k_h') = 4k_h/k_0 \quad . \quad (10)$$

If b' and c' are the concentrations, at time t, of isotopically normal and isotopically equilibrated inorganic phosphate then,

$$dc'/dt = k_h[a_0 - (b' + c')] + b'k_E^P \quad . \quad (11)$$

and
$$a_0 - (b' + c') = a_0 \exp - k_0 t \quad . \quad (12)$$

By eliminating b' between (11) and (12) a differential equation is obtained which can be integrated as for (6). Substitution by using (8), (9), and (10) then gives:

$$Q_P = \frac{4[(N_P R/N_S - 1)(k_0 - k_E^P) - (k_E^P \exp - k_0 t) + (k_0 \exp - k_E^P t)]}{k_0[(\exp - k_E^P t) - (\exp - k_0 t)]} \quad . \quad (13)$$

When k_E^M and k_E^P are zero, equations (7) and (13) reduce to $Q_O = N_M/N_S$ and $Q_P = 4N_P/N_S$ respectively.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, GOWER ST., LONDON, W.C.1.
[Present address (D. R. L.): CHEMISTRY DEPARTMENT,
AUCKLAND UNIVERSITY COLLEGE, NEW ZEALAND.]

[*Received, March 24th*, 1958.]

* In this particular case k_E^P is one-quarter of the rate coefficient for the oxygen exchange irrespective of labelling.

717. *The Reactions of Organic Phosphates. Part II.* The Hydrolysis of α-D-Glucose 1-(Dihydrogen Phosphate).*

By C. A. Bunton, D. R. Llewellyn, K. G. Oldham, and C. A. Vernon.

The rates of hydrolysis of α-D-glucose 1-phosphate in the range pH 1—8 can be interpreted in terms of two reactions, (*a*) involving the monoanion and proceeding with phosphorus–oxygen bond fission and (*b*) involving the neutral molecule and proceeding with carbon–oxygen bond fission. In strongly acidic media there is a rapid acid-catalysed reaction whose rate depends on Hammett's acidity function and which proceeds with carbon–oxygen bond fission. The mechanisms of these reactions are discussed.

Nomenclature. See Part I. Throughout this paper we use the name α-D-glucose 1-phosphate to denote species, ionic or non-ionic, in which one phosphate group is united to one α-D-glucose residue at the 1-position, *i.e.*, mono-α-D-glucose 1-phosphate.

α-D-Glucose 1-phosphate was chosen as the second substance for study in our investigation of the hydrolytic reactions of organic phosphates, first, because of the importance of sugar phosphates and, secondly, because it was hoped, in view of the known tendency for the pyranoside ring to separate as a carbonium ion, to observe S_N1 type reactions with carbon–oxygen bond fission.

From the literature [1] it is clear that α-D-glucose 1-phosphate is, typically of its class, rapidly hydrolysed in strongly acidic media. For example, Desjobert [2] studied its acid-catalysed hydrolysis at 1°, whereas with primary alkyl phosphates acid-catalysed hydrolysis can be conveniently studied only at much higher temperatures (cf. Part I). The reaction is, however, much slower in the range pH 1—8 than in strongly acid solutions and can, under these conditions, be studied at temperatures similar to those for simple alkyl phosphates.

The main features of the pH–rate profile have been established by Desjobert.[2] He found that the rate of hydrolysis increased slowly from pH 8 to pH 4 and then more rapidly as the pH decreased further. He concluded that between pH 4 and pH 1 the neutral species is the reactive entity. No systematic bond-fission studies have been reported, although Cohn,[3] using ^{18}O as tracer, showed that in the strongly acid region hydrolysis proceeds predominantly with carbon–oxygen bond fission.

The present paper reports an investigation by kinetic and isotopic techniques of the hydrolysis of α-D-glucose 1-phosphate over the range of acidities pH 8 to 3M-perchloric acid. Preliminary accounts of this work have been published.[4,5]

Experimental

α-D-Glucose 1-(dipotassium phosphate) was kindly supplied to us by Dr. E. M. Crook of the Biochemistry Department, University College, London. It had $[\alpha]_D^{23}$ +76·2° (*c* 1·0 in H_2O). A sample was also made by McCready and Hassid's method,[6] by using potato phosphorylase and purified by passage through Zeo-Karb 215 (to remove unwanted cations) and then absorbed on Amberlite IR-4B, from which it was eluted with 2N-potassium hydroxide. After treatment with decolorising charcoal the salt was crystallised from methanol–water. It had $[\alpha]_D^{25}$ +78·9° (*c* 1·0 in H_2O) (Found: P, 8·3. Calc. for $C_6H_{11}O_6{\cdot}PO_3K_2{,}2H_2O$: P, 8·3%).

Kinetics.—Runs were followed colorimetrically, by Allen's method for the estimation of

* Part I, preceding paper.

[1] Leloir, "Progress in the Chemistry of Natural Products," Vol. 8, 1951, p. 47.
[2] Desjobert, *Bull. Soc. Chim. biol.*, 1951, **33**, 42.
[3] Cohn, *J. Biol. Chem.*, 1949, **180**, 771.
[4] Barnard, Bunton, Llewellyn, Oldham, Silver, and Vernon, *Chem. and Ind.*, 1955, 760.
[5] Vernon, *Chem. Soc. Special Publ.*, No. 8, 1957, 17.
[6] McCready and Hassid, *J. Amer. Chem. Soc.*, 1944, **66**, 560.

inorganic phosphate,[7] or polarimetrically. Good first-order rate coefficients were obtained in each case, and the observed and the calculated infinity values agreed closely.

The following details are typical of experiments in which the rate of production of inorganic phosphate was determined. A solution containing the dipotassium salt ($1{\cdot}56 \times 10^{-3}$M) and perchloric acid (1·01M) was put in a thermostat at 25°. At appropriate times aliquot parts (5 c.c.) were removed and added to ice-cold water (13 c.c.). Sufficient 60% perchloric acid was added to bring the final strength to 0·72M; the colorimetric reagents were then added and the volume made up to 25 c.c. The solution was kept at 10° for 5 min., after which its optical density was measured in the usual way on a Hilger Spekker absorptiometer with a red filter (Kodak 608). Calculation showed that continuing hydrolysis of the substrate under the conditions of measurement introduced a negligible error into the rate coefficients and, in fact, the colour intensity was found to be sensibly constant for about 10 min. First-order rate coefficients, k_0, calculated as in Part I are shown below.

Time (min.)	O.D.	10^5k_0 (sec.$^{-1}$)	Time (min.)	O.D.	10^5k_0 (sec.$^{-1}$)
0	0·028	—	210	0·415	4·00
30	0·099	4·20	240	0·453	3·97
60	0·160	4·03	270	0·491	3·97
90	0·218	4·00	300	0·528	3·98
120	0·275	4·03	330	0·554	3·90
150	0·327	4·05	360	0·588	3·93
180	0·369	3·97	∞ (expt.)	1·005	—
			∞ (calc.)	1·005	—

The following details are typical of experiments in which the reaction was followed polarimetrically. A solution of the dipotassium salt (1·1367 g. in 25·2 c.c.) containing sulphuric acid (2·39M) was allowed to come to equilibrium in a 10 cm. jacketed polarimeter tube at 25°. Readings of the optical rotatory power were made at appropriate time intervals. The first-order rate coefficients k_0 are given below:

Time (min.)	$[\alpha]_D^{25}$	10^5k_0 (sec.$^{-1}$)	Time (min.)	$[\alpha]_D^{25}$	10^5k_0 (sec.$^{-1}$)
0	3·306°	—	45	2·420°	19·7
8	3·110	19·8	90	1·895	19·7
16	2·920	20·5	∞ (expt.)	1·149	—
26	2·720	19·8	∞ (calc.)	1·162	—
37	2·532	20·0			

Table 1 gives the first-order rate coefficients obtained in the range pH 8—1 at 82·0°. The reactions were all followed colorimetrically. The compositions of the buffers were similar to those given in Part I; the values of the pH were found, as before, from the data of Stene.[8]

The variation of rate coefficients with temperature was studied at each end of the pH range covered by Table 1. The results are given in Table 2.

TABLE 1. *Hydrolysis of* α-D-*glucose* 1-*phosphate at* pH 8—1.

pH	7·54	6·33	5·53	4·74	4·12	3·69	3·33	2·48	2·20	1·61	1·23
10^5k_0 (sec.$^{-1}$)	0·0253	0·106	0·212	0·360	0·635	1·50	3·43	20·7	38·9	175	467

TABLE 2.

pH	2·5	2·2	2·2	7·46	7·54
Temp.	100·1°	82·0°	25·0°	100·1°	82·0°
10^5k_0 (sec.$^{-1}$)	161	38·9	0·00877	0·288	0·0253

Table 3 gives the results obtained at 25·0° in strongly acidic media. Some of the runs were followed by rate of appearance of inorganic phosphate (substrate concentration *ca.* M/1000) and others polarimetrically (substrate concentration *ca.* M/10). The two methods gave sensibly similar results.

Isotope Experiments.—The positions of bond fission were determined, under various conditions, from the results of isotopic analysis of inorganic phosphate isolated from reactions run in water enriched with ^{18}O. The methods of isolation and isotopic analysis have already been described (Part I). Analysis of the other product of hydrolysis, glucose, would, of course, give no useful information since its rate of isotopic exchange is very rapid under all the relevant

[7] Allen, *Biochem. J.*, 1940, **34**, 858.
[8] Stene, *Rec. Trav. chim.*, 1930, **49**, 1133.

conditions. The results are shown in Table 4. As before, k_0 and k_E^P are the first-order rate coefficients, appropriate to the stated conditions, for hydrolysis of the substrate and for the exchange reaction of inorganic phosphate respectively; the symbols N_S and N_P refer

TABLE 3. *Hydrolysis of α-D-glucose 1-phosphate in strongly acid solution.*

Acid (M)	10^5k_0 (sec.$^{-1}$)	Acid (M)	10^5k_0 (sec.$^{-1}$)	Acid (M)	10^5k_0 (sec.$^{-1}$)	Acid (M)	10^5k_0 (sec.$^{-1}$)
0·51	1·65	2·01	12·2	3·00	28·7	0·93[c]	3·83[a]
1·01	4·00	2·11	11·7[a]	3·00[b]	43·9	1·54[c]	9·17[a]
1·16	4·13[a]	2·50	18·3	3·36	39·8	2·39[c]	20·0[a]
1·48	6·95						

[a] Polarimetric. [b] In 75% D_2O. [c] H_2SO_4 (all others $HClO_4$).

respectively to the excess abundance (atoms %) of tracer in the solvent and in the isolated inorganic phosphate; values of Q_P (the proportion of reaction proceeding by phosphorus–oxygen bond fission) have been calculated, except for the first two cases, by the equation given in Part I which allows for the subsequent exchange reaction of the inorganic phosphate.

TABLE 4. *Isotope results.*

Conditions	Time of heating (hr.)	10^5k_0 (sec.$^{-1}$)	$10^7k_E^P$ (sec.$^{-1}$)	N_S	N_P	Q_P (×100)
2M-$HClO_4$, 73·0°	1	—	—	0·72	0·00	0
pH 2·53, 82·0°	3·5	—	—	1·19	0·02	7
pH 4·18, ,, ...	57	0·635	1·17[a]	0·91	0·069	25
pH 6·3, ,, ...	380	0·106	1·17[a]	1·09	0·31	86

[a] Measured by Mr. V. A. Welch.

DISCUSSION

(a) *Reactions of the Monoanion and Neutral Species.*—Analysis of the kinetic data requires a knowledge of the dissociation constants of α-D-glucose 1-phosphate. The second dissociation constant has been accurately measured [9] as a function of temperature over the range 0—50°. Extrapolating these data gives the value pK_2 6·72 at 82·0°. The first dissociation constant is known less accurately; the value pK_1 1·23 is quoted [10] for 30°. It cannot, because of rapid hydrolysis of the substrate, be easily measured at higher temperatures. No great error will, however, be involved by using this value for the analysis of the present data.

The pH–rate profile for monomethyl phosphate in the range pH 2—8 can be accounted for, as shown in Part I, on the assumption that, in this range, reactions other than that involving the monoanion are unimportant. In the present case this assumption would clearly be wrong since from pH 5 to pH 1, where monoanion concentration must decrease, the rate increases in approximate proportion to the hydrogen-ion concentration.

Inspection of the shape of the profile (Fig. 1) suggests that the monoanion reaction occurs under the more alkaline conditions but is swamped, below pH 5, by some faster reaction. This view is supported by the isotope results which show that the predominating mechanisms at pH 6·3 and 2·5 must be different since they involve different modes of bond fission.

In solutions more acidic than pH 5 the dependence of rate on hydrogen-ion concentration suggests that the neutral species is, under these conditions, the reactive entity since its concentration, at least down to pH 2,* is approximately proportional to hydrogen-ion concentration and consequently proportionality between k_0 and c_{H^+} would be expected. The possibility that reaction proceeds *via* the conjugate acid of α-D-glucose 1-phosphate, *i.e.*, involves true acid-catalysis, can be excluded on the grounds that the

* The proportions of neutral species present at pH 5, 4, 3, and 2 are 0·00021, 0·0021, 0·021, and 0·176 respectively.

[9] Ashby, Clarke, Crook, and Datta, *Biochem. J.*, 1955, **59**, 203.
[10] Cori, Colowick, and Cori, *J. Biol. Chem.*, 1937, **121**, 465.

rate, in the region where the monoanion is the bulk component, would then be proportional to the square of the hydrogen-ion concentration.

If it is therefore accepted that the hydrolysis of α-D-glucose 1-phosphate in the range pH 2—8 can be represented as the sum of reactions proceeding *via* the neutral species (N) and the monoanion (M), the observed first-order rate coefficient at any given pH will be:

$$k_0 = \frac{C_N \cdot k_N}{C_P} + \frac{C_M \cdot k_M}{C_P} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where C_N and C_M are the concentrations of neutral and monoanion species respectively at that pH, C_P is the stoicheiometric concentration of organic phosphate, and k_N and k_M are the corresponding specific first-order rate coefficients. It remains to discover the best values of these coefficients. The simplest procedure is successive approximations as follows. At pH 2·2 the proportion of neutral species is 0·097; hence, assuming that at this relatively acid pH none of the rate is due to the monoanion gives an approximate value $3{\cdot}88 \times 10^{-4}/0{\cdot}097 = 4{\cdot}00 \times 10^{-3}$ sec.$^{-1}$ for the first-order rate coefficient (k_N) for the reaction of the neutral species. At pH 6·33 the proportion of neutral species present is very small (*ca.* 8×10^{-6}) and the rate coefficient arising from this would be $0{\cdot}32 \times 10^{-7}$ sec.$^{-1}$; the reaction at this pH mostly, therefore, involves the monoanion. The corresponding specific rate coefficient (k_M) can be obtained by subtracting from the observed value the small contribution due to the neutral species and dividing the result by the proportion of monoanion present: this gives $k_M = 1{\cdot}45 \times 10^{-6}$ sec.$^{-1}$. This " corrected " value can now be used to calculate values of k_N at several of the pH's studied. The results are given in Table 5. The constancy of the calculated values of k_N from pH 4·12 to 2·2

TABLE 5.

pH	4·12	3·69	3·33	2·48	2·20	1·61	1·23
$10^3 k_N$ (sec.$^{-1}$)	4·05	3·87	4·05	3·85	4·00	5·92	9·33

is good support for the view that in this region reaction is largely due to the neutral species. In Fig. 1 the rate profile calculated from equation 1 with the values k_N $3{\cdot}97 \times 10^{-3}$ sec.$^{-1}$ and k_M $1{\cdot}45 \times 10^{-6}$ sec.$^{-1}$ is seen to be in good agreement with the experimentally observed rate profile except below pH 2 where the observed rate is faster than predicted. The latter effect, which is reflected in the non-constancy of the values of k_N below pH 2 (Table 5), is clearly due to the contribution from a true acid-catalysed reaction.

The Arrhenius parameters for the two reactions can be calculated from the data in Table 2, after allowance has been made at the two pH's studied, for the amount of each reactant present. The results are: for the neutral species $E = 31{\cdot}0$ kcal. mole^{-1}, $A = 4{\cdot}30 \times 10^{16}$ sec.$^{-1}$; for the monoanion, $E = 30{\cdot}0$ kcal. mole^{-1}, $A = 5{\cdot}04 \times 10^{12}$ sec.$^{-1}$.

From equation (1) (and the assumption that the reactions of the monoanion and neutral species proceed with phosphorus–oxygen and carbon–oxygen bond fission respectively) the proportion of phosphorus–oxygen bond fission (Q_P) at any pH in the range pH 2—8 is given by:

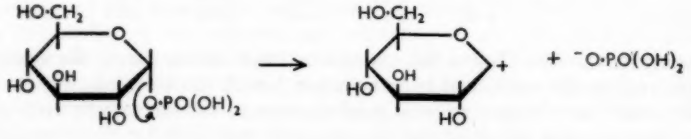
$$Q_P = C_M k_M / (C_M k_M + C_N k_N) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Using the values of k_M and k_N obtained above, the predicted values of Q_P at pH 2·53, 4·18, and 6·30 are respectively 0, 0·25, and 0·97. These are in fair agreement with the observed values of 0·07, 0·25, and 0·86 and it may be concluded that equations (1) and (2) together with the calculated values of k_N and k_M give an adequate account of the kinetic and isotope results for pH 2—8.

The specific rate coefficient and Arrhenius parameters for the hydrolysis of the monoanion of α-D-glucose 1-phosphate are not very different from the values of the corresponding quantities for monomethyl phosphate. As was pointed out in Part I, this is generally true; the kinetic parameters for hydrolysis of the monoanion do not vary much with the nature of the substituting group. Consequently, the mechanisms of hydrolysis of the

monoanions of monosubstituted phosphates are probably all very similar. A discussion for monomethyl phosphate has been given in Part I; the same discussion is relevant to α-D-glucose 1-phosphate, so will not be repeated.

The neutral species of α-D-glucose 1-phosphate is, on the other hand, much more reactive than that of monomethyl phosphate ($k_N = 3{\cdot}03 \times 10^{-2}$ sec.$^{-1}$ and $5{\cdot}0 \times 10^{-7}$ sec.$^{-1}$ respectively at 100·1°). *A priori*, the likely mechanisms are either a unimolecular [S_N1 (C)] or a bimolecular [S_N2 (C)] substitution at the $C_{(1)}$ atom of the pyranoside ring by a water molecule. The formal possibility that ring opening is involved is unlikely because such a process would require prior protonation of the ring oxygen atom (*i.e.*, would be acid-catalysed). There is, unfortunately, no direct kinetic criterion which is applicable for the determination of the molecularity. A strong argument, however, can be made for supposing the reaction to be unimolecular. It has been known for some time that aceto-halogeno-sugars readily undergo unimolecular replacement of halogen.[11] In a recent investigation, Rhind-Tutt [12] examined the conditions required for bimolecular substitution of a halogen atom at position 1 of the D-glucopyranoside ring. He found that 2 : 3 : 4 : 6-tetra-*O*-methyl-α-D-glucopyranosyl chloride underwent unimolecular substitution in methanol even in the presence of methoxide ions. The bimolecular process could be observed only in a solvent of lower dielectric constant (*e.g.*, propan-1-ol) and in the presence of a powerful nucleophile (*e.g.*, thiophenoxide ion). α-D-Glucose 1-phosphate, which has the same conformation as the compound studied by Rhind-Tutt, is therefore unlikely to undergo bimolecular substitution in water which has a high dielectric constant and a relatively low nucleophilic power. The situation is entirely analogous to that found for nucleophilic displacements of equatorial substituents in the *cyclo*hexane ring. The hydrolysis of the neutral species must, therefore, be interpreted as an S_N1(C) process, with slow heterolysis of the $C_{(1)}$–oxygen bond:



This type of process has not, so far as we are aware, previously been observed for any other organic phosphate. Its special facility in the present case is due to the large activation of the S_N1(C) process by the oxygen atom directly linked to the centre of substitution.[13]

(b) *The Reaction of the Conjugate Acid.*—In strongly acidic media the first-order rate coefficients (k_0) increase much more rapidly than stoicheiometric acidity (Table 3). However, log k_0 when plotted against Hammett's acidity function H_0 (values taken from Long and Paul [14]) for both sulphuric acid and perchloric acid gives a straight line of slope −0·94 (Fig. 2). This result taken in conjunction with the considerable increase in rate produced by change of solvent to deuterium oxide [15] means, on the Zucker–Hammett hypothesis, that the conjugate acid of α-D-glucose 1-phosphate, present in equilibrium concentration, undergoes covalency change in the rate-determining step of the reaction without the intervention of a solvent molecule.* The rate-determining step may be

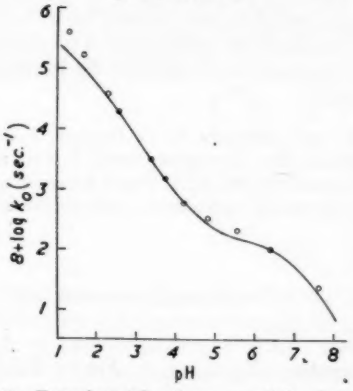
* The acid-catalysed reaction, as in the case of monomethyl phosphate, is accompanied by hydrolysis of the neutral species. However, the proportion of the latter reaction in M-perchloric acid is only *ca.* 2%, and since the correction would be much smaller than in the case of monomethyl phosphate and, because of the dependence of rate on H_0, more difficult to make, it has been neglected.

[11] Newth and Phillips, *J.*, 1953, 2896.
[12] Rhind-Tutt, Ph.D. Thesis, London, 1957.
[13] Ballinger, de la Mare, Kohnstam, and Prest, *J.*, 1955, 3641.
[14] Long and Paul, *Chem. Rev.*, 1957, **57**, 1.
[15] Bonhoeffer, *Trans. Faraday Soc.*, 1938, **34**, 252.

formulated, as in the case of the glycosides,[16] as the slow production of either a ring-closed ion (I) or a ring-opened ion (II), either of which would react rapidly to give the product.

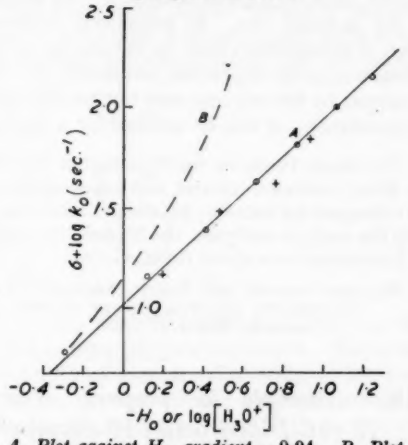
There is some reason for preferring the mechanisms involving (I); first, analogy with the mechanism of hydrolysis of the neutral species; and, secondly, a recent investigation by Rhind-Tutt [12] has shown that hydrolysis of glycosides is better interpreted as proceeding through intermediates of type (I) than of type (II). The reverse reaction (*i.e.*, combination

FIG. 1. *Hydrolysis of α-D-glucose 1-phosphate at 82·0°.*



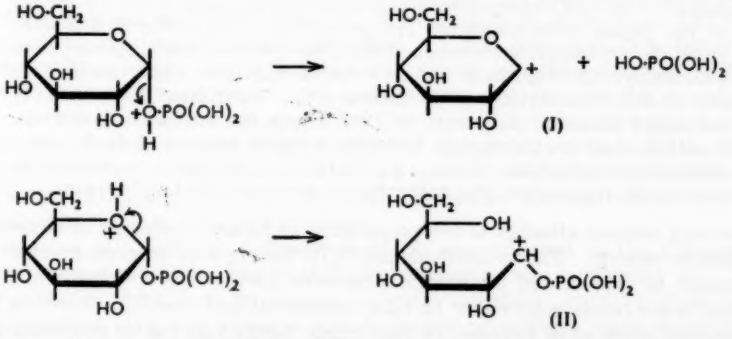
○, *Experimental values.* — *Calc. from equation* 1.

FIG. 2. *Acid-catalysed hydrolysis of α-D-glucose 1-phosphate at 25·0°.*



A, Plot against H_0, *gradient* −0·94. *B, Plot against* log $[H_3O]^+$. ○, *Colorimetric measurements.* +, *Polarimetric measurements.*

of phosphate and carbonium ion) is presumably unimportant since no difference in the rate of change of optical activity or appearance of inorganic phosphate was found.



(c) *Note on the Enzymic Hydrolysis of α-D-Glucose 1-Phosphate.*—Cohn,[3] in an important pioneer study of the enzymic hydrolysis of phosphates, first noticed that, whereas acidic hydrolysis of α-D-glucose 1-phosphate proceeds with carbon–oxygen bond fission, hydrolysis in the presence of prostatic acid phosphatase proceeds with phosphorus–oxygen bond fission. It is now known [17] that the result observed with the enzyme is a general one; whatever the substrate, hydrolysis with prostatic acid phosphatase always proceeds

[16] Bunton, Lewis, Llewellyn, and Vernon, *J.*, 1955, 4419.
[17] Bunton, Silver, and Vernon, *Proc. Chem. Soc.*, 1957, 348.

with phosphorus–oxygen bond fission. Cohn commented that her results were the first example in which it could be shown that an enzyme altered the reaction path. This statement is, perhaps, misleading. What the experiments actually show is that, for α-D-glucose 1-phosphate, the mechanisms of hydrolysis in acidic solution and in the presence of the enzyme are different. This is not surprising since the acidic mechanism arises from the structural features of the pyranoside ring whereas the enzymic mechanism involves the phosphate residue. Hydrolysis proceeding with phosphorus–oxygen bond fission in the absence of an enzyme can be realised, as shown above, with α-D-glucose 1-phosphate and reasons have been given elsewhere [17] for supposing that it is this reaction which is analogous to the enzymic one. In comparing enzymic and non-enzymic hydrolysis of phosphate esters it is important that, in the absence of the enzyme, reaction may proceed by a variety of reaction paths depending on conditions. In some instances the path which is specifically catalysed by the enzyme may not be experimentally realisable in its absence, for in certain circumstances, it will be masked by a readier reaction.

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WILLIAM RAMSAY AND RALPH FORSTER LABORATORY,
UNIVERSITY COLLEGE, GOWER STREET,
LONDON, W.C.1.

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718. *Attempts to prepare New Aromatic Systems. Part VII.** 15 : 16-*Dihydro*-15 : 16-*diazapyrene. The Synthesis of Di*(*pyridine*-2 : 6-*dimethylene*).

By WILSON BAKER, K. M. BUGGLE (née GALLAGHER), J. F. W. MCOMIE, and (in part) D. A. M. WATKINS.

The objective of the present work has been the preparation of a stable derivative (III) of *cyclo*tetradecaheptaene, as a contribution to our knowledge of the higher, even-membered *cyclo*polyolefins. Di(pyridine-2 : 6-dimethylene) (I), a tetrahydro-derivative of (III), has now been made, starting from 2-methylpyridine-6-aldehyde and 2 : 6-dimethylpyridine which condense to give 1 : 2-di-(6-methyl-2-pyridyl)ethylene (IV). The related di-*N*-oxide (V) rearranges in acetic anhydride to (VI), which by successive hydrolysis, reduction, and treatment with hydrogen bromide yields 1 : 2-di-(6-bromomethyl-2-pyridyl)ethane (VIII). Cyclisation to the new, ten-membered heterocyclic ring system (I) is best achieved by means of *n*-butyl-lithium.

CONSIDERABLE interest attaches to the preparation of higher vinylogues of benzene other than *cyclo*octatetraene. The *cyclo*polyolefins, C_nH_n (where n is an even number), which may formally be represented by Kekulé structures having closed systems of alternate double and single bonds, may either be fully conjugated and contain n identical, hybrid, carbon–carbon bonds as in benzene, or the olefinic bonds may fail to conjugate and the substance be accurately represented (except in conformation) by a Kekulé type formula as in *cyclo*octatetraene.[1,2] The Hückel rule[3] predicts that in this series of compounds only

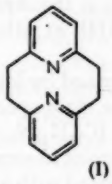
* Part VI, *J.*, 1957, 4026.

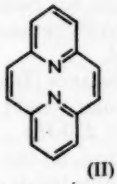
[1] Baker, "The Development of the Concept of Aromaticity" in "Perspectives in Organic Chemistry," Ed. Sir A. Todd, Interscience Publishers, 1956, p. 44.

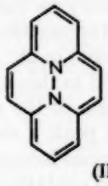
[2] Baker and McOmie, "Non-benzenoid Aromatic Compounds" in "Progress in Organic Chemistry," ed. J. W. Cook, Vol. III, pp. 48—49, Butterworths, 1955; "Cyclopolyolefines," in "Non-benzenoid Aromatic Compounds," ed. D. Ginsburg, Interscience Publ., 1958.

[3] Hückel, *Z. Physik*, 1931, **70**, 204.

those having $(4n + 2)$ π-electrons will be of general benzenoid character. Two reasons, however, make it unlikely that this prediction can be directly tested. First, *cyclo*polyolefins, $C_{10}H_{10}$, $C_{12}H_{12}$, $C_{14}H_{14}$, etc., if conjugated must have carbon–carbon bond angles close to 120° and be essentially planar, and the molecules therefore would have re-entrant angles with resultant severe steric clash between the interior hydrogen atoms.[2,4] There would be two such interior hydrogen atoms in *cyclo*decapentaene, and three in *cyclo*dodecahexaene; *cyclo*tetradecaheptaene would have four interior hydrogen atoms irrespective of whether the molecule was shaped as the periphery of anthracene, phenanthrene, or pyrene. Secondly, such *cyclo*polyolefins would probably undergo very ready transannular bridging with formation of polycyclic structures, and these might further pass by movement of hydrogen atoms or by dehydrogenation into the related benzenoid compounds.[5]


(I)


(II)


(III)

The present paper describes an approach to the slightly indirect solution to this problem by a device which could be applied to a number of *cyclo*polyolefins. The steric clash of interior hydrogen atoms, and the possibility of transannular bridging are both avoided by replacing, *e.g.*, in *cyclo*tetradecaheptaene, the four interior hydrogen atoms by two tervalent nitrogen atoms, as in 15 : 16-dihydro-15 : 16-diazapyrene (III), so that the molecule would possess a peripheral C_{14} conjugated system, which should be almost strainless, although it is possible that the two nitrogen atoms might be slightly displaced, one above and one below the plane of the fourteen carbon atoms.

A practicable synthesis of the tetrahydro-derivative of (III), namely, di(pyridine-2 : 6-dimethylene) (I), has now been achieved. Preliminary *X*-ray studies show that it may have a " stepped " molecule with slightly distorted pyridine rings as in the structurally very similar molecule of di-*m*-xylylene (I; having each N replaced by CH).[6,7] The properties of this compound (I) will be described in a later communication, but it may be observed now that loss of four hydrogen atoms should give di(pyridine-2 : 6-dimethine) (II), and that this might undergo movement of electrons so as to avoid the repulsion of the two lone electron pairs of the nitrogen atoms by allowing a direct linking of these atoms and formation of the essentially planar, peripheral, conjugated system in (III). Formulæ (II) and (III) must be regarded as two of the extreme canonical forms of this molecule, but it appears that (III) and the other identical Kekulé-like structure would be the most important contributors to the hybrid molecule.

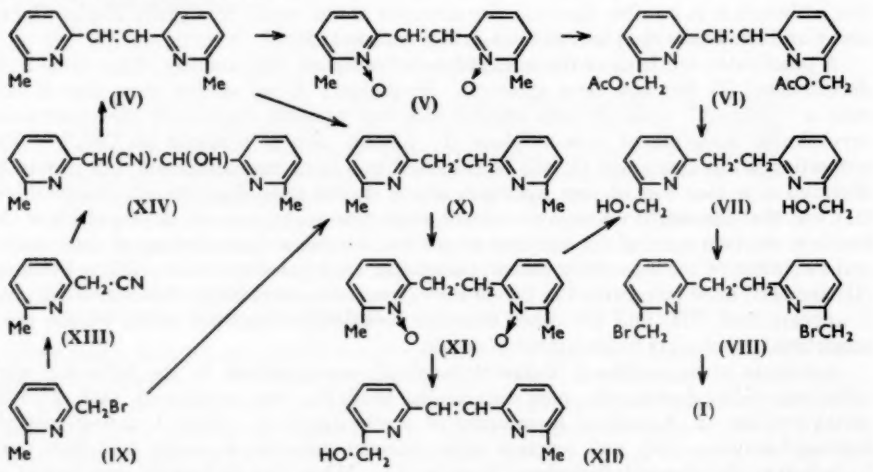
Synthesis of di(pyridine-2 : 6-dimethylene) (I) was achieved in the following way. 2-Methylpyridine-6-aldehyde, now technically available, was condensed with 2 : 6-dimethylpyridine (2 : 6-lutidine) in presence of acetic anhydride, giving 1 : 2-di-(6-methyl-2-pyridyl)ethylene (IV), and reaction with hydrogen peroxide in acetic acid then gave 1 : 2-di-(6-methyl-2-pyridyl)ethylene *N*-oxide (V). When the di-*N*-oxide was heated in acetic anhydride it underwent molecular rearrangement and diacetylation with formation of 1 : 2-di-(6-acetoxymethyl-2-pyridyl)ethylene (VI). In this reaction both oxygen atoms migrate to the adjacent methyl rather than to the methine groups, a behaviour which is consistent with the generalisation put forward by Boekelheide and Linn [8] that in these

[4] Mislow, *J. Chem. Phys.*, 1952, **20**, 1489.
[5] Prelog, Boarland, and Polyak, *Helv. Chim. Acta*, 1955, **38**, 434.
[6] Baker, McOmie, and Norman, *J.*, 1951, 1114.
[7] Brown, *J.*, 1953, 3278.
[8] Boekelheide and Linn, *J. Amer. Chem. Soc.*, 1954, **76**, 1286.

rearrangements migration of the oxygen atom of the *N*-oxide to the α-position of the side-chain in positions 2 or 6 occurs when at least two α-hydrogen atoms are available for replacement. Acid hydrolysis of the diacetoxy-compound (VI) yielded 1 : 2-di-(6-hydroxymethyl-2-pyridyl)ethylene which was reduced catalytically in presence of Adams catalyst to 1 : 2-di-(6-hydroxymethyl-2-pyridyl)ethane (VII). Reaction of (VII) with hydrogen bromide in acetic acid then gave 1 : 2-di-(6-bromomethyl-2-pyridyl)ethane (VIII).

Many experiments were carried out in order to remove the two atoms of bromine intramolecularly and thus effect cyclisation to di(pyridine-2 : 6-dimethylene) (I). These included a Wurtz–Fittig reaction with sodium in boiling xylene (which gave material of high molecular weight) and simultaneous slow addition to ether of the dibromide in ether–benzene and of phenyl-lithium in ether, under moderately high-dilution conditions. The second reaction gave an approximately 3% yield of di(pyridine-2 : 6-dimethylene) (I). By far the most satisfactory method which has been found is the slow addition of *n*-butyl-lithium to 1 : 2-di-(6-bromomethyl-2-pyridyl)ethane (VIII) in ether, which gives di-(pyridine-2 : 6-dimethylene) in 28% yield.

The structure assigned to this key substance (I) is confirmed by (*a*) elementary analysis, (*b*) accurate determination of the molecular weight in the mass spectrometer which gave for the most prominent peak a value of 210·184 ± 0·01 ($C_{14}H_{14}N_2$ requires *M*, 210·183, after allowance for the usual isotopic ratios), (*c*) the ultraviolet absorption spectrum which shows that the compound contains no double bonds conjugated with a pyridine ring, (*d*) the infrared spectrum which shows the absence of olefinic bonds apart from those which may be regarded as associated with the aromatic nuclei of the pyridine rings, and (*e*) *X*-ray crystallographical analysis. The *X*-ray analysis shows that the orthorhombic crystals, specific gravity 1·242, have *a* 13·48, *b* 11·26, *c* 7·41 Å, the mass in the unit cell being 842 equivalent to eight units of mass 105·25, or to four centrosymmetrical molecules of mass 210·5; the space group is Pcab.



A second approach to the preparation of the intermediate (IV) in the synthesis of the tricyclic compound (I) started from 2-hydroxymethyl-6-methylpyridine, which was either obtained technically or prepared by reducing methyl 6-methylpyridine-2-carboxylate with lithium aluminium hydride. The hydroxymethyl compound yielded 2-bromomethyl-6-methylpyridine (IX) when treated with hydrobromic acid, and with thionyl chloride it gave 2-chloromethyl-6-methylpyridine, converted by potassium cyanide into 2-cyanomethyl-6-methylpyridine (XIII). The methylene group of this 2-cyanomethyl compound is very reactive; in presence of piperidine it yields a benzylidene derivative,

1-cyano-1-(6-methyl-2-pyridyl)-2-phenylethylene, and condenses with 2-methylpyridine-6-aldehyde to give 1-cyano-1 : 2-di-(6-methyl-2-pyridyl)ethylene. When, however, the cyanomethyl compound is condensed with 2-methylpyridine-6-aldehyde, either in presence of *N*-ethylpiperidine, or by warming in its absence (these pyridine derivatives act as their own basic catalysts), the product is 2-cyano-1 : 2-di-(6-methyl-2-pyridyl)ethanol (XIV), which is dehydrated by acetic anhydride to the related olefin, 1-cyano-1 : 2-di-(6-methyl-2-pyridyl)ethylene (above), and undergoes dehydration, hydrolysis, and decarboxylation to give 1 : 2-di-(6-methyl-2-pyridyl)ethylene (IV) when boiled with hydrochloric acid. This preparation of (IV) is not as convenient as that previously described.

A third approach to the synthesis of compound (I) was by an alternative route to the intermediate 1 : 2-di-(6-hydroxymethyl-2-pyridyl)ethane (VII). 2-Bromomethyl-6-methylpyridine undergoes a Wurtz–Fittig reaction when treated with sodium, giving 1 : 2-di-(6-methyl-2-pyridyl)ethane (X) and this compound is also produced by the catalytic reduction of 1 : 2-di-(6-methyl-2-pyridyl)ethylene (IV). Treatment of (X) with hydrogen peroxide gave the di-*N*-oxide (XI) and when this was heated with acetic anhydride it gave two products. One of these was the *O*-acetyl derivative of 1-(6-hydroxymethyl-2-pyridyl)-2-(6-methyl-2-pyridyl)ethylene (XII), which had been formed as the result of the migration of one of the oxygen atoms to a methyl group, and of the other to a methylene group with subsequent loss of water to give the olefin. The other product obtained after hydrolysis was 1 : 2-di-(6-hydroxymethyl-2-pyridyl)ethane (VII), arising from migration of both oxygen atoms to the adjacent methyl groups, but the yield was not more than 5% and the method is therefore much inferior to that already described involving the rearrangement of the di-*N*-oxide of the olefin (V) in which migration of the oxygen atoms occurs solely to the adjacent methyl groups and not at all to the methine groups.

A number of other experiments in this same group of 2 : 6-disubstituted pyridines has been carried out during the course of this work, and these will be described briefly.

2 : 6-Bischloromethylpyridine, formed in good yield from 2 : 6-bishydroxymethylpyridine by treatment with thionyl chloride, yields 2 : 6-biscyanomethylpyridine with potassium cyanide in aqueous methanol. 2 : 6-Bisbromomethylpyridine is readily prepared from 2 : 6-bishydroxymethylpyridine by treatment with aqueous hydrobromic acid. Attempts to convert this 2 : 6-bisbromomethylpyridine into di(pyridine-2 : 6-dimethylene) (I) by treatment with sodium were unsuccessful; this contrasts with the behaviour of *m*-xylylene dibromide which is converted into di-*m*-xylylene in 12% yield by this method.[6] 2 : 6-Bisbromomethylpyridine is strongly dermatitic and lachrymatory; the related chloromethyl compound is lachrymatory.

An interesting result was obtained when the *N*-oxide of 2 : 6-bisacetoxymethylpyridine was heated with acetic anhydride: rearrangement occurred to give 2-acetoxymethyl-6-diacetoxymethylpyridine, hydrolysed by hydrochloric acid to 2-hydroxymethylpyridine-6-aldehyde.

2-Carboxy-6-methylpyridine gave an *N*-oxide with hydrogen peroxide, but rearrangement of this in presence of acetic anhydride was accompanied by the liberation of carbon dioxide, and the product was 2-acetoxymethylpyridine which is also formed by treating 2-methylpyridine *N*-oxide with acetic anhydride.[8]

Condensation of pyridine-2 : 6-dialdehyde with 2 : 6-dimethylpyridine in presence of acetic anhydride did not give the conjugated tri- or tetra-cyclic aromatic system (II) or (III) by a double condensation between one molecule of each reactant, but the dialdehyde reacted with two molecules of 2 : 6-dimethylpyridine, giving 2 : 6-di-[2-(6-methyl-2-pyridyl)vinyl]pyridine, probably as a mixture of geometrical isomers; it could be reduced to 2 : 6-di-[2-(6-methyl-2-pyridyl)ethyl]pyridine. The azine of 2-methylpyridine-6-aldehyde did not give 1 : 2-di-(6-methyl-2-pyridyl)ethylene (IV) when heated, but profound decomposition occurred.

The ultraviolet spectra of many of the derivatives of 2 : 6-dimethylpyridine are recorded in the Table. The derivatives of 1 : 2-di-(6-methyl-2-pyridyl)ethane (X), including

di(pyridine-2 : 6-dimethylene) (I), in which the two pyridine nuclei are united *via* saturated carbon atoms, possess a single, strong, absorption band at *ca.* 266 mμ; in the corresponding conjugated olefins, *e.g.*, 1 : 2-di-(6-methyl-2-pyridyl)ethylene (IV), this band is slightly more intense, and a second stronger band appears at *ca.* 318 mμ. This suggests that all these olefins have the same geometrical configuration, and, in view of the shape of the curves, the methods of preparation, and the failure to undergo isomerisation in the presence of hydrobromic acid, they are assumed to be the *trans*-isomers. The

Ultraviolet absorption spectra characteristics in ethanol.

Compound	$\lambda_{max.}$ (mμ)	$\log_{10} \varepsilon$	$\lambda_{max.}$ (mμ)	$\log_{10} \varepsilon$
Di(pyridine-2 : 6-dimethylene) (I)	274	3·68	—	—
2 : 6-Lutidine	264	3·50	—	—
1 : 2-Di-(6-methyl-2-pyridyl)ethane (X)	267·5	3·95	—	—
2 : 6-Di-[2-(6-methyl-2-pyridyl)ethyl]pyridine	*ca.* 210	4·30	268	4·28
			274	4·22
1 : 2-Di-(6-acetoxymethyl-2-pyridyl)ethane	266	3·52	—	—
1 : 2-Di(6-hydroxymethyl-2-pyridyl)ethane (VII)	266·5	3·85	—	—
1 : 2-Di-(6-methyl-2-pyridyl)ethane-1 : 2-diol (techn.)	266·5	3·91	—	—
2-Cyano-1 : 2-di-(6-methyl-2-pyridyl)ethanol (XIV)	255·5	3·53	—	—
1 : 2-Di-(6-methyl-2-pyridyl)ethane di-*N*-oxide (XI)	221	4·54	261	4·20
1 : 2-Di-(6-methyl-2-pyridyl)ethylene (IV)	265	4·16	318	4·58
1 : 2-Di-(6-acetoxymethyl-2-pyridyl)ethylene (VI)	266	4·15	317	4·49
1 : 2-Di-(6-hydroxymethyl-2-pyridyl)ethylene	265	4·12	318	4·48
1-(6-Hydroxymethyl-2-pyridyl)-2-(6-methyl-2-pyridyl)-ethylene (XII)	265	4·08	318	4·43
1-Cyano-1 : 2-di-(6-methyl-2-pyridyl)ethylene	222	3·38	266	3·17
			328	3·65
1 : 2-Di-(6-methyl-2-pyridyl)ethylene di-*N*-oxide (V)	220	4·50	—	—
	250	4·27	301	4·17
2 : 6-Di-[2-(6-methyl-2-pyridyl)vinyl]pyridine	266	4·35	303	4·48
			337	4·42
6-Methylpyridine-2-aldehyde	241	3·55	265	3·63
			271	3·61
Pyridine-2 : 6-dialdehyde	237	3·78	262	3·66
			267	3·67

presence of the two oxygen atoms in the di-*N*-oxides of these compounds makes no very marked alteration to the ultraviolet spectra.

Experimental

1 : 2-*Di*-(6-*methyl*-2-*pyridyl*)*ethylene* (IV).—(*a*) A mixture of 2-methylpyridine-6-aldehyde (5·5 g.), 2 : 6-dimethylpyridine (20 g.; redistilled, b. p. 142—143°), and acetic anhydride (5·5 ml.) was heated at 175—180° for 3 hr. The very dark product was distilled under reduced pressure and yielded a fraction, b. p. *ca.* 136—137°/0·4 mm., as a yellow oil which solidified (yield variable, 5—7 g.). Recrystallisation from ethanol gave pale yellow crystals, m. p. 109—111°, and further crystallisation from benzene gave 1 : 2-*di*-(6-*methyl*-2-*pyridyl*)*ethylene* as almost colourless needles or prisms, m. p. 111—113° (Found: C, 80·1; H, 6·6; N, 13·5. $C_{14}H_{14}N_2$ requires C, 80·1; H, 6·7; N, 13·3%). The substance shows a brilliant yellow fluorescence in ultraviolet light. The *dipicrate* prepared in ethanol and recrystallised from nitromethane gave yellow crystals, decomp. 235—266° (Found: C, 46·8; H, 3·0. $C_{14}H_{14}N_2.2C_6H_3O_7N_3$ requires C, 46·7; H, 3·0%).

(*b*) 2-Cyano-1 : 2-di-(6-methyl-2-pyridyl)ethanol (XIV) (see below) (1·0 g.) was boiled for 5 hr. with acetic acid (5 ml.) and concentrated hydrochloric acid (5 ml.), poured into excess of aqueous sodium hydroxide, and extracted with ether. The extracts yielded a product which separated from light petroleum (b. p. 40—60°) in needles (0·4 g.), m. p. and mixed m. p. 110—113°.

1 : 2-*Dibromo*-1 : 2-*di*-(6-*methyl*-2-*pyridyl*)*ethane*.—1 : 2-Di-(6-methyl-2-pyridyl)ethylene (IV) (2·5 g.) in chloroform (8 ml.) was treated with bromine (1·9 g.) in chloroform (5 ml.) at 0°, then kept at room temperature for 1 hr. The solvent was removed under reduced pressure, and the solid crystallised from dioxan and then from benzene, giving 1 : 2-*dibromo*-1 : 2-*di*-(6-*methyl*-2-*pyridyl*)*ethane* as colourless needles (3·8 g.), m. p. 194—196° (decomp.) (Found: C, 45·1; H, 3·8. $C_{14}H_{14}N_2Br_2$ requires C, 45·4; H, 3·8%).

1 : 2-*Di*-(6-*methyl*-2-*pyridyl*)*ethylene Di*-N-*oxide* (V).—1 : 2-Di-(6-methyl-2-pyridyl)ethylene (2 g.) in acetic acid (120 ml.) was heated at 70—80° with 30% aqueous hydrogen peroxide (2 ml.) for 3 hr., and heating then continued for a further 9 hr. after addition of more hydrogen peroxide (1·4 ml.). The mixture was then evaporated to *ca.* 40 ml. under diminished pressure and again after the addition of water (40 ml.) and extracted with chloroform. After treatment with potassium carbonate and drying ($MgSO_4$), distillation of the chloroform left a solid which was crystallised from ethanol–benzene, then benzene, and finally from ethanol, giving 1 : 2-*di*-(6-*methyl*-2-*pyridyl*)*ethylene di*-N-*oxide* (1·7 g.), m. p. 247·5—249° (decomp.) (Found: C, 69·0; H, 5·8. $C_{14}H_{14}O_2N_2$ requires C, 69·4; H, 5·8%).

1 : 2-*Di*-(6-*acetoxymethyl*-2-*pyridyl*)*ethylene* (VI).—A mixture of the preceding di-*N*-oxide (4·2 g.) and acetic anhydride (30 ml.) was heated on the steam-bath for 6 hr., then distilled to dryness under reduced pressure. The residue was crystallised several times from a small volume of ethanol (charcoal), yielding 1 : 2-*di*-(6-*acetoxymethyl*-2-*pyridyl*)*ethylene* as needles (2·8 g., 50%), m. p. 133—134° (Found: C, 66·2; H, 5·6; N, 8·9. $C_{18}H_{18}O_4N_2$ requires C, 66·3; H, 5·5; N, 8·6%). The overall yield from 1 : 2-di-(6-methyl-2-pyridyl)ethylene (*ca.* 35%) was not altered when the crude di-*N*-oxide, obtained directly from the oxidising mixture by evaporation to complete dryness, was used in this experiment.

1 : 2-*Di*-(6-*hydroxymethyl*-2-*pyridyl*)*ethylene*.—The preceding diacetoxy-compound (20 g.) was boiled for 10 hr. with concentrated hydrochloric acid (400 ml.), then cooled and neutralised by the addition of 30% aqueous sodium hydroxide (ice-cooling). The precipitate was collected, washed, and crystallised from ethanol, giving 1 : 2-*di*-(6-*hydroxymethyl*-2-*pyridyl*)*ethylene* as needles (12·0 g.), m. p. 142—144° (Found: C, 69·5; H, 5·7. $C_{14}H_{14}O_2N_2$ requires C, 69·4; H, 5·8%).

1 : 2-*Di*-(6-*hydroxymethyl*-2-*pyridyl*)*ethane* (VII).—1 : 2-Di-(6-hydroxymethyl-2-pyridyl)-ethylene (3·5 g.) in methanol (175 ml.) was shaken vigorously with hydrogen at 4 atm. for 10 hr. in presence of Adams platinum oxide (0·2 g.). The filtered mixture was concentrated (to *ca.* 40 ml.) and cooled, and the solid collected and crystallised from ethanol–ethyl acetate and then from ethanol, giving 1 : 2-*di*-(6-*hydroxymethyl*-2-*pyridyl*)*ethane* (*ca.* 2·3 g.) as prisms, m. p. 157—159° (Found: C, 68·9; H, 6·3; N, 11·5. $C_{14}H_{16}O_2N_2$ requires C, 68·9; H, 6·6; N, 11·5%). The *dipicrate* formed yellow plates (from acetone), m. p. 220—228° (decomp.) (Found: C, 44·9; H, 3·2. $C_{14}H_{16}O_2N_2,2C_6H_3O_7N_3$ requires C, 44·4; H, 3·1%).

1 : 2-*Di*-(6-*bromomethyl*-2-*pyridyl*)*ethane* (VIII).—1 : 2-Di-(6-hydroxymethyl-2-pyridyl)-ethane (5·0 g.) was added to a solution (35 ml.; 50% w/w) of hydrogen bromide in acetic acid, and the mixture was gently warmed to initiate an exothermic reaction, after which it was heated on the water-bath for 24 hr. The cooled solution was added to water and neutralised at 0° by aqueous sodium hydroxide, and the solid 1 : 2-di-(6-bromomethyl-2-pyridyl)ethane collected and crystallised from benzene–light petroleum (b. p. 60—80°), giving needles (6·6 g.), m. p. 118—120° (decomp.). The substance is not very stable owing to self-quaternisation.

Di(*pyridine*-2 : 6-*dimethylene*) (I).—The strength of a solution of *n*-butyl-lithium, prepared by Gilman's method,[9] was found by titration. This solution of *n*-butyl-lithium (1·1 mols.) was then added during 1 hr., with vigorous stirring in an atmosphere of nitrogen, to 1 : 2-di-(6-bromomethyl-2-pyridyl)ethane (VIII) (3·7 g.) suspended in ether (250 ml.), after which the mixture was boiled for ½ hr. A further quantity (*ca.* 0·5 mol.) of the ethereal *n*-butyl-lithium was then added during 2 hr. and boiling was continued for 1 hr. more. Addition of water and extraction with benzene yielded a solid (2·5 g.) which was sublimed at 140—150°/12 mm. (1·0 g.; m. p. 240—250°), and then crystallised from benzene giving *di*(*pyridine*-2 : 6-*dimethylene*) as colourless plates, m. p. 256—258° (0·75 g., 28%) (Found: C, 79·8; H, 7·0; N, 13·2. $C_{14}H_{14}N_2$ requires C, 80·0; H, 6·7; N, 13·3%).

2-*Hydroxymethyl*-6-*methylpyridine*.—Methyl 6-methylpyridine-2-carboxylate [10,11] (7·5 g.) in ether (50 ml.) was added during ½ hr. to a stirred solution of lithium aluminium hydride (3·8 g.) in ether (80 ml.); water (50 ml.) was then added dropwise and the mixture was filtered. The solid was suspended in hot methanol, saturated with carbon dioxide, boiled, and filtered. The combined ether and methanol filtrates were evaporated to dryness under diminished pressure, and the product taken up in ether, dried (K_2CO_3), and distilled at 105—110°/14 mm., giving a colourless oil (2·8 g.) which solidified as needles. The *picrate* separated from ethanol as yellow

[9] Gilman *et al.*, *J. Amer. Chem. Soc.*, 1949, **71**, 1499.
[10] Black, Depp, and Corson, *J. Org. Chem.*, 1949, **14**, 17.
[11] Mathes, Sauermilch, and Klein, *Chem. Ber.*, 1953, **86**, 584.

needles, m. p. 130—131° (Found: C, 44·1; H, 3·4. $C_{13}H_{12}O_6N_4$ requires C, 44·3; H, 3·4%). The *O*-acetyl derivative, prepared by boiling with acetic anhydride and sodium acetate for 2 hr., was characterised as the picrate, yellow needles (from ethanol), m. p. 114—115° (this acetyl derivative was prepared by Boekelheide and Linn,[8] by heating 2 : 6-dimethylpyridine *N*-oxide with acetic anhydride; picrate, m. p. 114—115°); hydrolysis of the *O*-acetyl derivative with boiling hydrochloric acid and basification regenerated 2-hydroxymethyl-6-methylpyridine.

2-Bromomethyl-6-methylpyridine (IX).—2-Hydroxymethyl-6-methylpyridine (9·0 g.) was boiled for ½ hr. with 48% aqueous hydrobromic acid (100 ml.), then cooled in ice, neutralised with concentrated aqueous sodium hydroxide, and extracted with ether. The dried ($MgSO_4$) extracts were evaporated at room temperature under diminished pressure leaving a strongly lachrymatory and dermatitic, partly crystalline mass (6·3 g., 60%) which was unstable even at room temperature, giving a red solid, but which could be kept in dry ethereal solution. The picrate formed yellow needles (from ethanol), m. p. 142—143°. Barnes and Fales [12] isolated 2-bromomethyl-6-methylpyridine as the picrate, m. p. 143°, in unstated but extremely low yield, from the product obtained by brominating 2 : 6-dimethylpyridine with *N*-bromosuccinimide.

2-Chloromethyl-6-methylpyridine.—To 2-hydroxymethyl-6-methylpyridine (1·6 g.) was slowly added thionyl chloride (30 ml.) at 0°, and the mixture was then warmed on the water-bath for 4 hr. Evaporation to dryness under reduced pressure gave a solid hydrochloride (m. p. 152—154°) which yielded a rather unstable, ether-soluble free base (1·5 g.), b. p. 45—50°/0·4 mm., which darkened when kept. The *picrate* of 2-chloromethyl-6-methylpyridine formed yellow plates (from ethanol), m. p. 161—162° (Found: C, 42·4; H, 3·0; N, 14·9. $C_{13}H_{11}O_7N_4Cl$ requires C, 42·1; H, 3·0; N, 15·1%).

2-Cyanomethyl-6-methylpyridine (XIII).—2-Chloromethyl-6-methylpyridine hydrochloride (5 g.) in methanol (50 ml.) was heated on the steam-bath for 2 hr. with potassium cyanide (5·0 g.) in water (20 ml.), basified with saturated aqueous sodium carbonate and extracted with ether. The extracts yielded a product which was distilled *in vacuo*, giving an oil (2·5 g.) which, after crystallisation from light petroleum (b. p. 40—60°) followed by sublimation at 70—80°/20 mm., formed needles, m. p. 40—41°. This 2-cyanomethyl-6-methylpyridine undergoes change when kept, and was characterised as the *picrate*, yellow needles (from alcohol), m. p. 179—180° (decomp.) (Found: C, 46·8; H, 3·0; N, 19·1. $C_{14}H_{11}O_7N_5$ requires C, 46·5; H, 3·0; N, 19·1%).

1-Cyano-1-(6-methyl-2-pyridyl)-2-phenylethylene.—2-Cyanomethyl-6-methylpyridine (1·0 g.) and benzaldehyde (0·9 g.) were boiled for 2 hr. in ethanol (12 ml.) containing piperidine (0·5 ml.). Distillation then yielded an oil (1·1 g.), b. p. 135°/0·3 mm., which solidified, and after recrystallisation from light petroleum (b. p. 60—80°) the 1-cyano-1-(6-methyl-2-pyridyl)-2-phenylethylene was obtained as colourless crystals, m. p. 51—52°. The *picrate* formed yellow needles (from ethanol), m. p. 148—149° (Found: C, 56·2; H, 3·6. $C_{15}H_{12}N_2,C_6H_3O_7N_3$ requires C, 56·1; H, 3·3%).

Condensation of 2-Cyanomethyl-6-methylpyridine with 2-Methylpyridine-6-aldehyde.—(a) *In presence of piperidine.* A mixture of the cyanomethyl compound (2·0 g.) and the aldehyde (1·5 g.) in ethanol (30 ml.) containing piperidine (0·5 ml.) was boiled for 2 hr. Distillation then gave an oil, b. p. 155—160°/0·3 mm., which solidified and was crystallised from light petroleum (b. p. 60—80°), giving *1-cyano-1 : 2-di-(6-methyl-2-pyridyl)ethylene* as needles (2·1 g.), m. p. 82—84° (Found: C, 76·3; H, 5·4; N, 18·4. $C_{15}H_{12}N_2$ requires C, 76·6; H, 5·5; N, 17·8%). The substance is unstable in acid solution.

(b) *In presence of N-ethylpiperidine.* A similar experiment to the above was carried out but with *N*-ethylpiperidine in place of piperidine. Removal of the alcohol left a solid which was crystallised from benzene and then from light petroleum (b. p. 100—120°), giving *2-cyano-1 : 2-di-(6-methyl-2-pyridyl)ethan-1-ol* (XIV) as needles (2·2 g.), m. p. 118—120° (Found: C, 71·3; H, 6·0; N, 16·2. $C_{15}H_{14}ON_2$ requires C, 71·1; H, 5·9; N, 16·6%).

(c) *By heat.* The cyanomethyl compound (1·1 g.) and the aldehyde (1·0 g.) were mixed with gentle warming. After 10 min. at room temperature the mass solidified; crystallisation from benzene gave 2-cyano-1 : 2-di-(6-methyl-2-pyridyl)ethanol (XIV) (1·53 g.), m. p. and mixed m. p. 118—120°.

Dehydration of 2-Cyano-1 : 2-di-(6-methyl-2-pyridyl)ethanol.—The hydroxy-compound (0·5 g.) was boiled for ½ hr. with acetic anhydride (4 ml.) and acetic acid (2 ml.), and the mixture

[12] Barnes and Fales, *J. Amer. Chem. Soc.*, 1953, **75**, 3830.

poured into aqueous sodium hydroxide and extracted with ether. The ethereal solution yielded 1-cyano-1 : 2-di-(6-methyl-2-pyridyl)ethylene (0·2 g.), m. p. and mixed m. p. 82—84°.

1 : 2-*Di*-(6-*methyl*-2-*pyridyl*)*ethane* (X).—(*a*) 2-Bromomethyl-6-methylpyridine (10 g.) was boiled vigorously for 5 hr. in anhydrous xylene (350 ml.) with powdered sodium (7 g.). The cooled mixture was filtered, the black solid was washed with fresh xylene, and the combined filtrates were distilled, leaving an oil which solidified. This was sublimed twice at 120°/14 mm. giving 1 : 2-*di*-(6-*methyl*-2-*pyridyl*)*ethane* (X) as needles (1·8 g., 40%), m. p. 48—49°, b. p. 100—102°/0·25 mm. (Found : C, 79·5; H, 7·3; N, 12·9. $C_{14}H_{16}N_2$ requires C, 79·5; H, 7·5; N, 13·2%). The *dipicrate* was prepared from alcoholic solution and recrystallised from nitromethane in yellow plates, m. p. 268° (decomp. from 254°) (Found: C, 46·5; H, 3·3; N, 16·3. $C_{14}H_{16}N_2,2C_6H_3O_7N_3$ requires C, 46·6; H, 3·3; N, 16·7%).

(*b*) 1 : 2-Di-(6-methyl-2-pyridyl)ethylene (IV) (6·0 g.) was hydrogenated in methanol for 3 hr. at 1 atm. in presence of Adams platinum oxide (0·1 g.). Filtration and isolation as described in paragraph (*a*) gave 1 : 2-di-(6-methyl-2-pyridyl)ethane (5·5 g.), m. p. and mixed m. p. 48—49°.

1 : 2-*Di*-(6-*methyl*-2-*pyridyl*)*ethane Di*-N-*oxide* (XI).—A mixture of 1 : 2-di-(6-methyl-2-pyridyl)ethane (2·5 g.), acetic acid (14 ml.), and 30% aqueous hydrogen peroxide (2·3 ml.) was heated at 70—80° for 3 hr., more hydrogen peroxide (1·7 ml.) then added and heating continued for a further 9 hr. The mixture was evaporated to small bulk under reduced pressure, and again after the addition of water (20 ml.), and the solid product then collected and recrystallised first from ethanol–ethyl acetate and then from benzene, giving 1 : 2-*di*-(6-*methyl*-2-*pyridyl*)-*ethane di*-N-*oxide* (1·4 g.), m. p. 183—185° (Found: C, 68·1; H, 6·8. $C_{14}H_{16}O_2N_2$ requires C, 68·9; H, 6·6%).

Rearrangement of 1 : 2-*Di*-(6-*methyl*-2-*pyridyl*)*ethane Di*-N-*oxide*.—The di-*N*-oxide (XI) (4·5 g.) and acetic anhydride (15 ml.) were heated on the steam-bath for 9 hr., and the product distilled, giving a yellow oil (3·6 g.), b. p. 160—170°/0·2 mm. This oil had an ultraviolet absorption spectrum very similar to that of 1 : 2-di-(6-methyl-2-pyridyl)ethylene, and a derived *picrate*, yellow needles, m. p. 190—191°, from alcohol, is probably that of 1-(6-acetoxymethyl-2-pyridyl)-2-(6-methyl-2-pyridyl)ethylene (Found: C, 53·1; H, 4·1. $C_{16}H_{16}O_2N_2,C_6H_3O_7N_3$ requires C, 53·1; H, 3·8%). A portion of the oil (2·7 g.) was hydrolysed with boiling hydrochloric acid (60 ml.) for 8 hr., the solution basified with strong aqueous potassium hydroxide and extracted with ether, and the product distilled at *ca.* 180°/0·3 mm., giving a viscous yellow oil (1·2 g.) which solidified. The solid was shaken several times with a little ether, and the insoluble material was crystallised twice from ethanol–ethyl acetate, giving 1 : 2-di-(6-hydroxymethyl-2-pyridyl)ethane (VII) (0·2 g.), m. p. and mixed m. p. 156—158° (ultraviolet absorption spectra were identical). The ether-soluble product was recovered and extracted with boiling light petroleum (b. p, 60—80°), evaporation of which left a solid which was crystallised from benzene, giving colourless crystals (0·78 g.), m. p. 89—91°, probably 1-(6-*hydroxymethyl*-2-*pyridyl*)-2-(6-*methyl*-2-*pyridyl*)*ethylene* (XII) (Found: C, 74·6; H, 6·0; N, 12·2. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2; N, 12·4%).

2 : 6-*Bischloromethylpyridine*.—Thionyl chloride (150 ml.) was slowly added to 2 : 6-bishydroxymethylpyridine (10 g.) at 0°, and the mixture was warmed on the water-bath for 4 hr., then cooled, and treated with benzene. The precipitated hydrochloride (10·5 g.) was collected, washed with benzene, dried, dissolved in water, and neutralised with sodium hydrogen carbonate. The 2 : 6-*bischloromethylpyridine* was collected and crystallised from light petroleum (b. p. 40—60°) as needles (8·0 g.), m. p. 74—75° (Found: C, 47·9; H, 4·0; N, 8·3. $C_7H_7NCl_2$ requires C, 47·7; H, 4·0; N, 7·9%).

2 : 6-*Biscyanomethylpyridine*.—A mixture of 2 : 6-bischloromethylpyridine hydrochloride (6·5 g.), potassium cyanide (6·5 g.), water (20 ml.), and methanol (70 ml.) was heated on the water-bath for 5 hr. After addition of water (100 ml.) and saturation with sodium carbonate, ether-extraction yielded a solid which was crystallised from ethanol (charcoal), giving 2 : 6-*biscyanomethylpyridine* as needles (0·7 g., 28%), m. p. 97—98° (Found: C, 68·6; H, 4·6; N, 27·0. $C_9H_7N_3$ requires C, 68·8; H, 4·5; N, 26·8%). This biscyano-compound was similarly obtained in 40% yield from 2 : 6-bisbromomethylpyridine hydrobromide.

2 : 6-*Bisbromomethylpyridine*.—2 : 6-Bishydroxymethylpyridine (20 g.) and 48% aqueous hydrobromic acid (200 ml.) were boiled for 2 hr., and the mixture was then neutralised at 0° by the addition of a concentrated aqueous solution of sodium hydroxide. The solid product was collected, washed, and recrystallised from light petroleum (b. p. 40—60°), giving 2 : 6-bisbromomethylpyridine as needles or prisms (24 g., 62%), m. p. 84—89° (Found: C, 31·8; H, 2·5; N,

XUM

5·6. Calc. for $C_7H_7NBr_2$: C, 31·7; H, 2·7; N, 5·3%). Barnes and Fales [14] prepared this compound from 2 : 6-dimethylpyridine (*a*) in 1% yield by treatment with phenyl-lithium and then bromine and (*b*) in 2% yield by reaction with *N*-bromosuccinimide; they record m. p. 66—76° or 66—99° according to the rate of heating; the indeterminate m. p. is due to intermolecular quaternisation.

2 : 6-*Bisacetoxymethylpyridine* N-*Oxide*.—2 : 6-Bishydroxymethylpyridine (5 g.; technical) was boiled for 3 hr. with acetic anhydride (20 ml.) and anhydrous sodium acetate (5 g.), then distilled to dryness under reduced pressure, and the residue extracted with hot chloroform, filtered, and distilled, giving 2 : 6-diacetoxymethylpyridine (6·0 g.), b. p. 110—113°/0·1 mm. This substance (22·0 g.) was oxidised with 30% aqueous hydrogen peroxide (20·0 ml.) in acetic acid (60 ml.) at 70—80° for 3 hr.; hydrogen peroxide solution (7 ml.) was then added, heating continued for 9 hr., and the mixture cooled. The 2 : 6-*di*(*acetoxymethyl*)*pyridine* N-*oxide* which separated (5·0 g.) was collected and recrystallised from ethanol as needles, m. p. 141—143° (Found: C, 55·0; H, 5·9. $C_{11}H_{13}O_5N$ requires C, 55·2; H, 5·4%). The filtrate was concentrated twice to small bulk after addition of water (2 × 25 ml.) and extracted with chloroform, and the extracts were treated with saturated, aqueous potassium carbonate, dried ($MgSO_4$), and distilled, giving a further amount (10 g.) of the crude *N*-oxide.

2-*Hydroxymethylpyridine*-6-*aldehyde*.—Unpurified 2 : 6-di(acetoxymethyl)pyridine *N*-oxide (15·6 g.) was warmed on the steam-bath for 14 hr. with acetic anhydride (36 ml.); the mixture was next distilled *in vacuo*, yielding 2-*acetoxymethyl*-6-*diacetoxymethylpyridine* (12·0 g.), b. p. 158—159°/0·5 mm. (Found: N, 5·0. $C_{13}H_{15}O_6N$ requires N, 5·0%). This afforded the *oxime* of 2-acetoxymethylpyridine-6-aldehyde as needles (from ethanol), m. p. 179—180° (Found: C, 55·2; H, 5·0; N, 13·9. $C_9H_{10}O_3N_2$ requires C, 55·7; H, 5·2; N, 14·4%). Hydrolysis of 2-acetoxymethyl-6-diacetoxymethylpyridine by boiling concentrated hydrochloric acid, evaporation to small bulk, addition of potassium carbonate, and extraction with chloroform, gave 2-*hydroxymethylpyridine*-6-*aldehyde* as a cloudy oil (3·8 g., 70%), b. p. 80—86°/0·1 mm. (Found: N, 10·4. $C_7H_7O_2N$ requires N, 10·2%). The aldehyde is hygroscopic and when kept changes to a pale yellow solid which leaves a residue when distilled *in vacuo*; the 2 : 4-*dinitrophenylhydrazone*, crystallised from ethanol and then from ethyl acetate, forms deep yellow needles, m. p. 233° (Found: C, 49·3; H, 3·3. $C_{13}H_{11}O_5N_5$ requires C, 49·2; H, 3·5%).

2-*Carboxy*-6-*methylpyridine* N-*Oxide*.—2-Carboxy-6-methylpyridine [12] (2·5 g.), acetic acid (11 ml.), and 30% aqueous hydrogen peroxide (2 ml.) was heated at 70—80° for 3 hr., more hydrogen peroxide (1·5 ml.) then added, and heating continued for 9 hr. The solid was collected from the cooled mixture and recrystallised from ethanol, giving 2-*carboxy*-6-*methylpyridine* N-*oxide* as needles (1·8 g., 64%), m. p. 176° (Found: C, 54·8; H, 4·8; N, 9·1. $C_7H_7O_3N$ requires C, 54·9; H, 4·5; N, 9·2%). A further amount (0·3 g.) was obtained from the acetic acid filtrate. This *N*-oxide was also obtained in 85% yield when 2-methoxycarbonyl-6-methylpyridine was oxidised in the same manner.

2-*Acetoxymethylpyridine*.—2-Carboxy-6-methylpyridine *N*-oxide (3·2 g.) was heated on the steam-bath for 8 hr. with acetic anhydride (5 ml.). The solution was next distilled under reduced pressure, giving 2-acetoxymethylpyridine (2·6 g., 80%), b. p. 120—121°/23 mm.; the picrate formed yellow needles (from ethanol), m. p. 166—168° (Found: C, 44·2; H, 3·2; N, 15·1. Calc. for $C_{14}H_{12}O_9N_4$: C, 44·2; H, 3·2; N, 14·7%). Boekelheide and Linn [8] prepared the compound by treating 2-methylpyridine *N*-oxide with acetic anhydride, and record b. p. 115—118°/22 mm., and picrate, m. p. 168°.

2 : 6-*Di*-[2-(6-*methyl*-2-*pyridyl*)*vinyl*]*pyridine*.—Pyridine-2 : 6-dialdehyde (1·5 g.; tech.), 2 : 6-dimethylpyridine (7·5 g.), and acetic anhydride (1·5 g.) were kept at 175° for 3 hr., the acetic anhydride removed under reduced pressure, and the residue crystallised twice from the minimum volume of benzene (charcoal). 2 : 6-*Di*-[2-(6-*methyl*-2-*pyridyl*)*vinyl*]*pyridine* was obtained as needles (0·8 g.), m. p. 148—156°, falling to 129—133° on further crystallisation from benzene (Found: C, 80·7; H, 6·0; N, 13·0. $C_{21}H_{19}N_3$ requires C, 80·5; H, 6·0; N, 13·4%). This compound is almost certainly a mixture of two geometrical isomerides and perhaps also of different conformational forms.

2 : 6-*Di*-[2-(6-*methyl*-2-*pyridyl*)*ethyl*]*pyridine*.—The preceding compound (0·2 g.) was hydrogenated in methanol for 6 hr. in presence of Adams platinum oxide catalyst. Filtration, evaporation, and crystallisation from light petroleum (b. p. 40—60°) gave 2 : 6-*di*-[2-(6-*methyl*-2-*pyridyl*)*ethyl*]*pyridine* as needles, m. p. 108—109° (Found: C, 79·5; H, 7·4; N, 13·5. $C_{21}H_{23}N_3$ requires C, 79·5; H, 7·2; N, 13·2%).

2-Methylpyridine-6-aldazine.—2-Methylpyridine-6-aldehyde (2·4 g.; tech.) was warmed with hydrazine hydrate (0·5 g.) and the solid was collected and crystallised from ethanol, giving the *azine* as yellow needles (2·5 g.), m. p. 175—176° (Found: C, 70·3; H, 5·9; N, 23·7. $C_{14}H_{14}N_4$ requires C, 70·6; H, 5·9; N, 23·5%). It decomposes and darkens above its m. p., but 1 : 2-di-(6-methyl-2-pyridyl)ethylene could not be isolated from the decomposition products.

The authors thank the Royal Commission for the Exhibition of 1851 for an overseas Scholarship (to K. M. B.), and Imperial Chemical Industries Limited for the determination of the molecular weight of compound (I) in the mass spectrometer (through the kindness of Dr. M. A. T. Rogers), for its infrared spectrum measurements (Mr. J. F. Grove, Akers Research Laboratories), and for its *X*-ray crystallographical measurements (Dr. C. J. Brown, Blackley).

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719. *The Rearrangement of Sulphinic Esters.*

By A. H. WRAGG, J. S. MCFADYEN, and T. S. STEVENS.

Further observations support the view that the isomerisation of certain sulphinic esters to the corresponding sulphones is mainly an intermolecular process involving ionisation of the ester.

ARCUS, BALFE, and KENYON [1] studied the conversion of α-methylbenzyl toluene-*p*-sulphinate (I) into α-methylbenzyl *p*-tolyl sulphone (II) and concluded that the process was in part intramolecular, but mainly dependent on ionisation of the ester. Later, Cope, Morrison, and Field [2] effected the rearrangement of allyl benzenesulphinate and related compounds, without reaching a final decision on the mechanism. The results now reported emphasise the intermolecular and no doubt ionic character of the change.

(I) *p*-$C_6H_4Me{\cdot}S(:O){\cdot}O{\cdot}CHMePh$ $\qquad$ *p*-$C_6H_4Me{\cdot}S(:O)(\rightarrow O){\cdot}CHMePh$ (II)

Sulphones were prepared from the related sulphinic acid and alcohol ($R{\cdot}SO_2H + HOR' \longrightarrow R{\cdot}SO_2R'$) in three ways: (1) by heating the acid and alcohol in acetic acid–hydrochloric acid,[3] (2) by heating the related sulphinic ester in the same medium; and (3) by thermal rearrangement of the ester alone or in an inert solvent. None of these processes is of general application and in each individual case they give substantially the same result (Table 1).

Experiments with diphenylmethyl compounds support the formulations:

$$R{\cdot}SO_2H + R'{\cdot}OH \longrightarrow R{\cdot}SO_2^- + R'{\cdot}OH_2^+ \longrightarrow R{\cdot}SO_2^- + R^+ + H_2O \longrightarrow R{\cdot}SO_2R' + H_2O \quad (1)$$

$$R{\cdot}SO{\cdot}OR' + H^+ \longrightarrow R{\cdot}SO{\cdot}\underset{H}{O}{}^+R' \longrightarrow R{\cdot}SO_2H + R'^+ \longrightarrow$$

$$H^+ + R{\cdot}SO_2^- + R'^+ \longrightarrow H^+ + R{\cdot}SO_2R' \quad (2)$$

$$R{\cdot}SO{\cdot}OR' \longrightarrow R{\cdot}SO_2^- + R'^+ \longrightarrow R{\cdot}SO_2{\cdot}R' \quad (3)$$

The synthesis of sulphone from alcohol and sulphinic acid proceeds easily in acetic acid, nitromethane, acetonitrile, benzene, or toluene; but rearrangement of the ester takes place only in the first two solvents. Rearrangement, however, is observed in the remaining solvents in presence of a little toluene-*p*-sulphinic acid; it does not proceed in acetonitrile in presence of sodium toluene-*p*-sulphinate. It would appear that rearrangement is favoured by ionising solvents (including the homogeneous ester itself) and availability of protons. The sulphone is also produced from diphenylmethyl methyl ether and toluene-*p*-sulphinic acid in nitromethane or toluene, but not from diphenylmethanol and methyl toluene-*p*-sulphinate.

The intermolecular character of the reaction was further shown by " mixing experiments." When diphenylmethyl toluene-*p*-sulphinate was heated in acetic acid containing

[1] Arcus, Balfe, and Kenyon, *J.*, 1938, 485.
[2] Cope, Morrison, and Field, *J. Amer. Chem. Soc.*, 1950, **72**, 59.
[3] Hinsberg, *Ber.*, 1917, **50**, 468.

TABLE 1.

R	R′	Yield (%) of sulphone by method (1)	(2)	(3)
p-Tolyl	Methyl	0	0	0
,,	Phenyl	0	0	0
,,	Benzyl	0	0	0
,,	*o*-Nitrobenzyl	0	0	0
,,	α-Methylbenzyl	20	20	20—30
,,	αα-Dimethylbenzyl	90	86	87
,,	Diphenylmethyl	90	93	100
,,	*p*-Chlorodiphenylmethyl	80	89	95
,,	Phenyl-*o*-tolylmethyl	90	90	95
,,	Phenyl-*p*-tolylmethyl	80	82	80
p-Chlorophenyl	Diphenylmethyl	90	93	100

p-chlorobenzenesulphinic acid, some *p*-chlorophenyl diphenylmethyl sulphone was produced; the same ester and *p*-chlorodiphenylmethanol gave a mixture of sulphones which contained chlorine but from which no *p*-chlorodiphenylmethyl *p*-tolyl sulphone could be isolated. Clear evidence was obtained of the formation of dichlorinated and chlorine-free sulphones when a mixture of *p*-chlorodiphenylmethyl toluene-*p*-sulphinate and phenyl-*p*-tolylmethyl *p*-chlorobenzenesulphinate was heated without a solvent.

The following inequalities in the rates of rearrangement of homogeneous esters were observed qualitatively; αα-dimethylbenzyl toluene-*p*-sulphinate > α-methylbenzyl toluene-*p*-sulphinate; phenyl-*o*-tolylmethyl toluene-*p*-sulphinate > diphenylmethyl toluene-*p*-sulphinate; diphenylmethyl *p*-chlorobenzenesulphinate > diphenylmethyl toluene-*p*-sulphinate. A rate-determining ionisation is consistent with these observations.

EXPERIMENTAL

All identifications of known solids were supported by mixed melting points.

Alcohols.—*p*-Chlorodiphenylmethanol [4] and phenyl-*o*-tolylmethanol [5] were prepared by published methods and phenyl-*p*-tolylmethanol [6] (12·5 g.; m. p. 58°) from benzaldehyde (14·7 g.) and the Grignard reagent from *p*-bromotoluene (25 g.) and magnesium (3·35 g.).

Toluene-p-*sulphinic Esters.*—Toluene-*p*-sulphinyl chloride [7] was freed from solvents and thionyl chloride at 0·05 mm. at room temperature and used at once without distillation. The chloride (1·03 mol.), in a little dry ether, was added slowly to the alcohol (1 mol.) in pyridine (1·15 mol.) at 0° with shaking and addition of more ether as required to facilitate mixing. After additions of ether and 2N-hydrochloric acid the separated ether layer was washed thoroughly with dilute hydrochloric acid, sodium hydrogen carbonate solution, and water, and dried (12 hr.; Na_2SO_4). Removal of the ether *in vacuo* left the ester in good yield; see Table 2.

TABLE 2. *Toluene*-p-*sulphinic esters.*

Ester	Description	M. p.	Formula	Found, S %	Reqd., S %
Methyl [8]	Oil	(b. p. 129—130°/ 14 mm.)	$C_8H_{10}O_2S$	—	—
Phenyl	Unstable needles	51—52°	$C_{13}H_{12}O_2S$	—	—
Benzyl	Needles	22—24	$C_{14}H_{14}O_2S$	13·1	13·0
o-Nitrobenzyl	Needles	58—59	$C_{14}H_{13}O_4NS$	10·8	11·0
αα-Dimethylbenzyl	Oil	—	$C_{16}H_{18}O_2S$	11·5	11·7
Diphenylmethyl	Needles from EtOH	84	$C_{20}H_{18}O_2S$	9·9	9·9
Phenyl-*o*-tolylmethyl	Needles from EtOH	68—70	$C_{21}H_{20}O_2S$	9·4	9·5
p-Chlorodiphenylmethyl	Oil	—	$C_{20}H_{17}O_2SCl$	9·4	9·0
9-Fluorenyl	Prisms from Et_2O	107—108	$C_{20}H_{16}O_2S$	9·8	10·0

p-*Chlorobenzenesulphinyl chloride* was prepared by adding the sulphinic acid [9] (3 g.) to thionyl chloride (1·35 mol.) in ether (2 ml.). After the vigorous reaction, solvent and excess of

[4] Tschitschibabin and Schesler, *Chem. Zentr.*, 1926, I, 919.
[5] Tschitschibabin, *Chem. Zentr.*, 1910, I, 30.
[6] Cf. Marshall *et al.*, *J.*, 1915, **107**, 516, 894.
[7] Phillips, *J.*, 1925, 2569.
[8] Cf. Arndt and Scholtz, *Annalen*, 1934, **510**, 62.
[9] Knoevenagel and Kenner, *Ber.*, 1908, **41**, 3320.

thionyl chloride were removed at 0·2 mm. pressure, and the residual oil was kept for 6 hr. over potassium hydroxide in a vacuum desiccator (Found: Cl, 36·9. $C_6H_4OSCl_2$ requires Cl, 36·4%). It yielded in the usual way *diphenylmethyl* p-*chlorobenzenesulphinate*, needles, m. p. 83—84° from ether–ligroin (Found: S, 9·2. $C_{19}H_{15}O_2SCl$ requires S, 9·3%); and *phenyl*-p-*tolylmethyl* p-*chlorobenzenesulphinate*, a slightly yellow oil (Found: S, 8·6. $C_{20}H_{17}O_2SCl$ requires S, 9·0%).

Methyl, phenyl, benzyl, and *o*-nitrobenzyl *p*-toluenesulphinate did not give sulphone at temperatures below those leading to gross decomposition; the fluorenyl ester changed above 120° into an amorphous solid from which no homogeneous substance was isolated. Sulphones were formed from the α-methylbenzyl and αα-dimethylbenzyl esters slowly in the cold, more rapidly when heated, purer specimens being more stable. Rearrangement of the diarylmethyl esters took place, more reproducibly, above 100°. In a typical experiment α-methylbenzyl toluene-*p*-sulphinate (1·7 g.), acetic acid (4 ml.), and concentrated hydrochloric acid (0·15 ml.) were boiled for 1 hr. The product was dissolved in benzene and washed with alkali; the neutral material recovered by evaporation gave α-methylbenzyl *p*-tolyl sulphone (0·32 g.) from methanol–benzene. The same sulphone was synthesised by boiling α-methylbenzyl alcohol (1 g.), toluene-*p*-sulphinic acid (0·7 g.), acetic acid (4 ml.), and concentrated hydrochloric acid (0·15 ml.) for 1 hr. and isolating the product in the same way.

Diphenylmethyl *p*-tolyl sulphone was also prepared by heating diphenylchloromethane (5 g.) and sodium toluene-*p*-sulphinate (5 g.) in alcohol (40 ml.) under reflux for 3 hr.; the sulphone crystallised on cooling.

"*Mixing Experiments.*"—(1) Diphenylmethyl toluene-*p*-sulphinate (1 g.) and *p*-chlorobenzenesulphinic acid (0·1 g.) in acetic acid (2·5 ml.) were boiled for 15 min. The first crop of needles (0·85 g.), m. p. 186°, containing a trace of chlorine, was diphenylmethyl *p*-tolyl sulphone: the second crop gave, after four crystallisations from ethanol–acetone, *p*-chlorophenyl diphenylmethyl sulphone, m. p. 176—179° (Found: C, 67·0; H, 4·8; S, 8·8; Cl, 9·9. Calc. for $C_{19}H_{15}O_2SCl$: C, 66·5; H, 4·4; S, 9·3; Cl, 10·4%).

(2) Diphenylmethyl toluene-*p*-sulphinate (1 g.), *p*-chlorodiphenylmethanol (0·1 g.), and acetic acid (2·5 ml.) were boiled for 15 min.; successive crops of crystals were substantially diphenylmethyl *p*-tolyl sulphone containing a little chlorine; no *p*-chlorodiphenylmethyl *p*-tolyl sulphone could be isolated.

TABLE 3. *Sulphones*, $R{\cdot}SO_2{\cdot}R'$.

R	R′	Crystalln. solvent	M. p.	Formula	Found, S (%)	Reqd., S (%)
αα-Dimethylbenzyl	*p*-Tolyl	EtOH	144—145°	$C_{16}H_{18}O_2S$	11·5	11·7
Diphenylmethyl	*p*-Tolyl	EtOH	188—189	$C_{20}H_{18}O_2S$	9·7	9·9
Phenyl-*o*-tolylmethyl	*p*-Tolyl	EtOH	127—128	$C_{21}H_{20}O_2S$	9·3	9·5
Phenyl-*p*-tolylmethyl	*p*-Tolyl	MeOH–$COMe_2$	157	$C_{21}H_{20}O_2S$ [a]	9·5	9·5
p-Chlorodiphenylmethyl	*p*-Tolyl	MeOH–$COMe_2$	142	$C_{20}H_{17}O_2SCl$ [b]	9·3	9·0
Diphenylmethyl	*p*-Chlorophenyl	MeOH–$COMe_2$	177	$C_{19}H_{15}O_2SCl$ [c]	9·7	9·3
Phenyl-*p*-tolylmethyl	*p*-Chlorophenyl	MeOH–$COMe_2$	173	$C_{20}H_{17}O_2SCl$ [d]	9·2	9·0
p-Chlorodiphenylmethyl	*p*-Chlorophenyl	MeOH	126	$C_{19}H_{14}O_2SCl_2$ [e]	9·0	8·5

Additional analyses: [a] Found: C, 74·8; H, 5·8. Required: C, 75·0; H, 6·0%. [b] Found: C, 67·5; H, 4·75; Cl, 9·9. Required C, 67·4; H, 4·8; Cl, 10·0%. [c] Found: C, 66·1; H, 4·3; Cl, 10·8. Required: C, 66·5; H, 4·4; Cl, 10·4%. [d] Found: C, 67·3; H, 4·8; Cl, 10·4. Required: C, 67·4; H, 4·8; Cl, 10·0%. [e] Found: C, 60·4; H, 3·5. Required C, 60·5; H, 3·7%.

(3) Phenyl-*p*-tolylmethyl *p*-chlorobenzenesulphinate (0·6 g.) and *p*-chlorodiphenylmethyl toluene-*p*-sulphinate (0·6 g.) were heated for 12 min. at 160°. The pale green melt crystallised when rubbed with ether, and was recrystallised from acetone–methanol. The second crop (A) had m. p. 142—143° (Found: C, 71·5; H, 5·6; S, 9·2; Cl, 2·7%). The mother liquors were evaporated and the residue crystallised successively from acetone–methanol, ligroin, and methanol, the more soluble fraction being retained in each case; the final mixture (B) had m. p. 110—120° (Found: C, 64·5; H, 4·4; S, 8·8; Cl, 13·2%). The carbon : sulphur ratios show that no significant quantities of disulphoxides were present; the chlorine values demonstrate the presence of chlorine-free sulphone in (A) and dichlorinated sulphone in (B).

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720. *The Preparation of 7- and 9-Ribofuranosyl Derivatives of 8-Azaxanthine. A Note on the Preparation of 9-Glucopyranosylxanthine.*

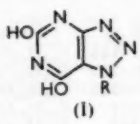
By J. Baddiley, J. G. Buchanan, and G. O. Osborne.

The 7- and the 9-β-D-ribofuranoside of 8-azaxanthine (I and II; R = ribofuranosyl) have been synthesised by the action of potassium hypobromite on 1-β-D-ribofuranosyl-1 : 2 : 3-triazole-4 : 5-dicarboxyamide (III; R = ribofuranosyl, R′ = NH_2).

In a re-examination of a similar reaction on glucosylglyoxaline-4 : 5-dicarboxyamide (V; R = glucopyranosyl) it is found that both the 7- and the 9-isomer of β-D-glucopyranosylxanthine (VI and IV; R = glucopyranosyl) are formed.

Since certain 8-azapurine bases function as purine antagonists in various biological systems, the synthesis and biological examination of the corresponding nucleosides is clearly of interest. The preparation of tri-*O*-benzoyl-β-D-ribofuranosyl azide in this Laboratory has led to a synthetic route to *N*-glycosyl derivatives (I and II; R = glycosyl) of 8-azaxanthine. The preparation by this route of 7- and 9-β-D-glucopyranosyl and β-D-xylopyranosyl derivatives of 8-azaxanthine has already been described.[1] The synthesis of the 7- and the 9-β-D-ribofuranosyl derivative of 8-azaxanthine is now reported.

Dimethyl acetylenedicarboxylate and 2 : 3 : 5-tri-*O*-benzoyl-β-D-ribofuranosyl azide[2] gave dimethyl 1-(2 : 3 : 5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1 : 2 : 3-triazole-4 : 5-dicarboxylate (III; R = ribofuranosyl, R′ = OMe). With methanolic ammonia at 0° this compound yielded 1-β-D-ribofuranosyl-1 : 2 : 3-triazole-4 : 5-dicarboxyamide (III; R = ribofuranosyl, R′ = NH_2). Reaction of the diamide with an excess of potassium hypobromite yielded the 7- and the 9-β-D-ribofuranosyl derivative of 8-azaxanthine (I and II; R = ribofuranosyl), separated by adsorption on a Dowex-2 (formate) column and elution with 0·2M-ammonium formate: complete removal of the 9-isomer required the passage of a large volume of eluate.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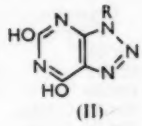
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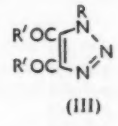
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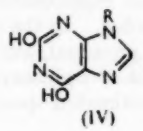
7-β-D-Ribofuranosyl-8-azaxanthine possessed spectroscopic properties similar to those recorded for the corresponding xylose and glucose derivatives;[1] the spectroscopic properties of 9-β-D-ribofuranosyl-8-azaxanthine resembled those of 9-β-D-glucopyranosyl-8-azaxanthine and of 9-β-D-xylopyranosyl-8-azaxanthine. The 7- and the 9-ribofuranosyl derivative had generally similar R_F values in two chromatographic systems. In ultraviolet light the 7-isomer was detected as a blue-fluorescent spot after exposure of the chromatograms to ammonia. The 9-isomer was detected as a similar fluorescent spot after exposure to hydrochloric acid fumes.

Very recently, Davoll[3] reported the preparation of *N*-glycosyl derivatives of several 8-azapurine bases through chloromercuri-derivatives. 8-Azaxanthosine (II; R = ribofuranosyl) was synthesised and the position of the ribose established conclusively. A sample, kindly provided by Dr. J. Davoll, is indistinguishable from one of our isomers, to which we had assigned the 9-ribosyl structure, in its spectra and on paper chromatography. Our orientation scheme,[1] based on spectroscopic comparison with a methylated 8-azaxanthine, is thus confirmed. Davoll has prepared three *N*-ribosyl derivatives of

[1] Baddiley, Buchanan, and Osborne, *J.*, 1958, 1651.
[2] Baddiley, Buchanan, Hodges, and Prescott, *J.*, 1957, 4769.
[3] Davoll, *J.*, 1958, 1593.

8-azaguanine. One was 8-azaguanosine. In the absence of appropriate reference compounds the others were described provisionally as 8- and 7-ribosyl-8-azaguanine. Treatment with nitrous acid converted the latter into a product spectroscopically similar to our 7-glycosyl derivatives of 8-azaxanthine.* The structures assigned provisionally are thus confirmed.

Xanthosine (IV; R = ribofuranosyl),[4] 9-D-ribopyranosylxanthine,[5] 9-D-mannopyranosylxanthine,[5] and 9-D-xylopyranosylxanthine [6] have been prepared from the appropriate 1-glycosylglyoxaline-4 : 5-dicarboxyamide (V; R = glycosyl) by treatment with potassium hypobromite. Attempts to prepare 9-D-glucopyranosylxanthine in a similar way were unsuccessful [6] and the 9-D- and 9-L-arabinopyranosyl diamide yielded only traces of glycosyl-purines. In the 8-azapurine field we have observed that the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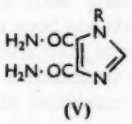
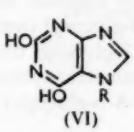

(V)


(VI)

1-β-D-glucopyranosyl as well as the 1-β-xylopyranosyl and 1-β-D-ribofuranosyl derivative of 1 : 2 : 3-triazole-4 : 5-dicarboxyamide give *N*-glycosyl derivatives of 8-azaxanthine on treatment with potassium hypobromite. In view of this, and of the probable similarity of the cyclisation step in the purine series, the failure of the route to the glucopyranosylpurine was surprising. Consequently, the reaction of 1-β-D-glucopyranosylglyoxaline-4 : 5-dicarboxyamide with an equivalent of potassium hypobromite was re-examined.

In small-scale experiments 1-D-xylopyranosyl- † and 1-D-glucopyranosyl-glyoxaline-4 : 5-dicarboxyamide were treated with potassium hypobromite (approx. 1 mol.). The reaction conditions were those previously employed for the preparation of 9-D-xylopyranosylxanthine.[6]

Products were examined by paper chromatography in propan-1-ol–ammonia (*d* 0·88)–water (6 : 3 : 1). On chromatograms, the xyloside reaction mixture displayed a prominent spot, detected by its ultraviolet absorption, at R_F 0·34. The glucoside reaction mixture displayed a counterpart at R_F 0·33. The areas corresponding to these spots were cut out, the materials eluted, and the ultraviolet absorption spectra in aqueous solution at pH 7 and in 0·1N-sodium hydroxide were recorded. The spectra of the two compounds were identical, the pairs of maxima in 0·1N-alkali being similar to those recorded for 9-D-xylopyranosylxanthine. The major products represented by the spots thus appeared to be 9-D-xylopyranosyl- and 9-D-glucopyranosyl-xanthine, respectively.

9-D-Glucopyranosylxanthine was isolated from a larger-scale preparation by ion-exchange chromatography on a Dowex-2 (formate) column, elution being carried out with ammonium formate at pH 5·8. The major product yielded xanthine and glucose (both identified by paper chromatography) on hydrolysis in acid. It ran as a single compound on paper in several solvents and showed absorption maxima in the ultraviolet region typical of a 9-substituted xanthine.[4-7] Its mode of preparation from 1-D-glucopyranosylglyoxaline-4 : 5-dicarboxyamide, itself prepared from 2 : 3 : 4 : 6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, implies that it is a β-glucosyl compound.[8]

Two minor components were eluted from the column in the above experiment. One of these showed only general ultraviolet absorption over the range 220—280 mμ and was not further investigated. The other component was of considerable interest. In two

* Communication from Dr. J. Davoll.
† Prepared by Dr. J. Stewart.

[4] Howard, McLean, Newbold, Spring, and Todd, *J.*, 1949, 232.
[5] Baxter, McLean, and Spring, *J.*, 1948, 523.
[6] Baxter and Spring, *J.*, 1947, 378.
[7] Gulland, Holiday, and Macrae, *J.*, 1934, 1639.
[8] Haynes and Newth, *Adv. Carbohydrate Chem.*, 1955, **10**, 207.

chromatographic systems it had the same R_F as 9-β-D-glucopyranosylxanthine. Moreover, as in the latter case, treating the paper chromatogram with hydrogen chloride fumes before viewing it in ultraviolet light led to the appearance of a blue fluorescent spot in place of the opaque spot previously observed. On acid hydrolysis, xanthine and glucose were produced (both detected on paper chromatograms) but rather more slowly than from 9-β-D-glucopyranosylxanthine. The absorption spectrum in 0·1N-hydrochloric acid consisted of a single maximum at 267 mμ, and in 0·1N-sodium hydroxide of a maximum at 290 mμ. These values agree well with those recorded for 7-methylxanthine.[7] The product was present in insufficient quantity to permit isolation of a pure sample, but it was clearly a 7-glucosylxanthine (VI; R = glucopyranosyl).

Although the reaction between glycosylglyoxaline-4 : 5-dicarboxyamides and hypobromite is potentially capable of yielding both 7- and 9-glycosides of xanthine, the preparation only of 9-glycosyl compounds has been recorded. In the light of the present work it is clear that 7-glycosyl compounds may also be produced, but in small quantity. A rough spectrophotometric estimation indicated a yield of 7-glucosylxanthine of about 2%. The yield of 9-β-D-glucopyranosylxanthine, also estimated spectrophotometrically, was 25%.

Since 5-amino-1-glucosylglyoxaline-4-carboxyamide and its isomers are also possible reaction products, the aqueous washings from the Dowex-2 column were examined. The complex mixture present appeared to contain no appreciable amount of these substances.

Experimental

Dimethyl 1-(2 : 3 : 5-*Tri*-O-*benzoyl*-β-D-*ribofuranosyl*)-1 : 2 : 3-*triazole*-4 : 5-*dicarboxylate*.—Dimethyl acetylenedicarboxylate (2·5 g., 1·25 mol.) in dry benzene (100 c.c.) was heated under reflux for 5 hr. with 2 : 3 : 5-tri-*O*-benzoyl-β-D-ribofuranosyl azide [2] (6·7 g., 1 mol.), and the solution poured into an excess of light petroleum (b. p. 40—60°). The precipitated gum (9·7 g.) was chromatographed in benzene on neutral alumina, 4 : 1 benzene–chloroform being used for elution. Fractions 5—19 (each of 100 c.c.) contained the triazole derivative. Fractions 7—19 were evaporated to a colourless gum (6·5 g.). For analysis the 1 : 2 : 3-*triazole derivative* was converted into a foam (Found: C, 61·3; H, 4·2; N, 6·9. $C_{32}H_{27}O_{11}N_3$ requires C, 61·0; H, 4·3; N, 6·7%).

1-β-D-*Ribofuranosyl*-1 : 2 : 3-*triazole*-4 : 5-*dicarboxyamide*.—Dimethyl 1-(2 : 3 : 5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1 : 2 : 3-triazole-4 : 5-dicarboxylate (6·5 g.) in dry methanol (180 c.c.) saturated with ammonia was kept at 0° for 4 days. After concentration of the solution to half its volume, crystals (1·75 g.) separated on cooling. Further evaporation followed by the addition of an excess of ether precipitated a further quantity of solid (0·4 g.). Recrystallised from methanol the *diamide* had $[\alpha]_D^{20}$ −64° (*c* 1·03 in water) (Found: C, 37·8; H, 4·8; N, 24·3. $C_9H_{13}O_6N_5$ requires C, 37·6; H, 4·6; N, 24·4%). It consumed 0·94 mol. of periodate.

Reaction with hypobromite. 1-β-D-Ribofuranosyl-1 : 2 : 3-triazole-4 : 5-dicarboxyamide (0·621 g.) was treated with freshly prepared potassium hypobromite [5] (12 c.c.) at 2° for 20 hr. and at 70° for 15 min. The product was percolated down a Dowex-2 resin column (18 × 1 cm., 200—400 mesh) in the formate form, which was washed with water and then eluted with 0·2M-ammonium formate at pH 7. Fractions 58—90 (each of 25 c.c.), containing the 7-isomer, were combined. Fractions 112—300, containing the 9-isomer, were also combined.

7-β-D-*Ribofuranosyl*-8-*azaxanthine* (5 : 7-*Dihydroxy*-1-β-D-*ribofuranosyl*-v-*triazolo*[4 : 5-d]-*pyrimidine*).—Fractions 58—90 from the previous experiment were evaporated at 35° (rotary evaporator) and ammonium formate was sublimed under reduced pressure at 65°. The residual gum was dissolved in water and adsorbed on a column of " Norit " charcoal. This was washed with water (to remove inorganic impurities) and the product eluted with ethanol–ammonia (*d* 0·88)–water (40 : 1 : 50). Removal of the solvent left a gum which crystallised readily (47 mg.). Recrystallised from aqueous methanol, the 7-β-D-*ribofuranosyl derivative* had m. p. 185°, $[\alpha]_D^{20}$ −92° (*c* 0·5 in water) (Found: C, 37·9; H, 4·3. $C_9H_{11}O_6N_5$ requires C, 37·9; H, 3·9%). It consumed 0·94 mol. of periodate. The total yield of material estimated spectrophotometrically was 191 mg.

9-β-D-*Ribofuranosyl*-8-*azaxanthine* (5 : 7-*Dihydro*-3-β-D-*ribofuranosyl*-v-*triazolo*[4 : 5-d]-*pyrimidine*).—Fractions 112—300 from the earlier experiment were evaporated at 35°. The

considerable quantity of ammonium formate remaining was extracted with small quantities of dry methanol. Removal of solvent from these extracts, followed by sublimation of ammonium formate, gave a brown gum. This was adsorbed on charcoal and eluted with ethanol–ammonia (*d* 0·88)–water as before. Removal of solvent left a colourless gum. This was dissolved in ethanol, and ether was added to precipitate a white solid (about 10 mg.) (Found: C, 34·7; H, 4·8. $C_9H_{11}O_6N_5,1\frac{1}{2}H_2O$ requires C, 34·6; H, 4·5%). The amount of *product* present initially was 82 mg., estimated spectrophotometrically.

Hydrolysis. N-Hydrochloric acid (0·2 c.c.) was added to the ribofuranosyl derivative (0·5 mg.). Hydrolysis to 8-azaxanthine and ribose was complete in 1 hr. at 100°. Hydrolysates were examined by paper chromatography in the systems: *A*, propan-1-ol–ammonia (*d* 0·88)–water (6 : 3 : 1); and *B*, the water-poor phase from butan-1-ol–acetic acid–water (4 : 1 : 5).

	R_F values in solvents		Conditions for fluorescence
	A	B	
7-β-D-Ribofuranosyl-8-azaxanthine	0·35	0·28	Alkaline
9-β-D-Ribofuranosyl-8-azaxanthine	0·38	0·31	Acid
,, ,, ,, (from Davoll)	0·38	0·31	Acid
8-Azaxanthine	0·31	0·45	Acid
Ribose	0·59	0·29	—

8-Azaxanthine and its derivatives were detected by their fluorescence under the appropriate conditions. Ribose was detected by the aniline phthalate spray.

Determination of the Ring Size.—The method previously described [9] was employed in the examination of 1-β-D-ribofuranosyl-1 : 2 : 3-triazole-4 : 5-dicarboxyamide, 7-β-D-ribofuranosyl-8-azaxanthine, and 9-β-D-ribofuranosyl-8-azaxanthine. Periodate oxidation, followed by reduction with sodium borohydride and acid hydrolysis, gave glycerol (detected on paper chromatograms) and no ethylene glycol. This confirms the ribofuranosyl structure for these compounds.

Spectra of Azaxanthine Derivatives.—These maxima (mμ) were as tabulated. The figures in parentheses are extinction coefficients (ε).

	In HCl, pH 2·2	pH 7·0	In 0·1N-NaOH
7-β-D-Ribofuranosyl-8-azaxanthine	278(5·3 × 10³)	278(5·0 × 10³)	310(5·1 × 10³)
9-β-D-Ribofuranosyl-8-azaxanthine	(*a*) 255(8·9 × 10³)	252(8·6 × 10³)	250(5·6 × 10³)
	240(6·7 × 10³)	277(7·9 × 10³)	280(8·4 × 10³)
	(*b*) 256(9·5 × 10³)	252(9·7 × 10³)	251(7·1 × 10³)
	240(5·9 × 10³)	277(8·8 × 10³)	280(9·5 × 10³)

(*a*) Prepared from sugar azide; determination carried out on 1 mg. sample. (*b*) Reported by Davoll.[2]

9-β-D-*Glucopyranosylxanthine.*—1-Glucopyranosylglyoxaline-4 : 5-dicarboxyamide [6] (1·0 g.) was treated with freshly prepared potassium hypobromite [5] (6 c.c.; approx. 1 mol.) at 2° for 1 hr., then at 70° for 10 min. The product was diluted with water (50 c.c.) and percolated down a Dowex-2 column (15 × 1 cm.; 200—400 mesh) in the formate form. The column was washed with water (500 c.c.), and products were eluted with 0·1M-ammonium formate solution at pH 5·8. Fractions 5—7 (each of 50 c.c.) and 14—17 contained minor components. Fractions 23—32, containing the major component, were combined and evaporated to dryness at 35°. Ammonium formate was sublimed at 60° under reduced pressure. The residue was dissolved in water (5 c.c.), and the solution filtered. Addition of an excess of ethanol led to the precipitation of a cream-coloured powder (149 mg.). This material was redissolved in water, followed by reprecipitation with ethanol. The 9-*glucoside* was dried for 18 hr. at 70° (Found: C, 39·7; H, 5·3; N, 16·9. $C_{11}H_{14}O_7N_4,H_2O$ requires C, 39·8; H, 4·9; N, 16·9%).

Ultraviolet absorption maxima were at 234 (ε 7·1 × 10³) and 262 mμ (ε 7·6 × 10³) in 0·1N-hydrochloric acid, and at 248 (ε 8·7 × 10³) and at 277 mμ (ε 7·6 × 10³) in 0·1N-sodium hydroxide.

7-*Glucopyranosylxanthine.*—Fractions 5—7 from the earlier experiment were combined and evaporated, and ammonium formate was sublimed as previously described. A small amount of coloured material remained. This had a maximum at 267 mμ in 0·1N-hydrochloric acid and at 290 mμ in 0·1N-sodium hydroxide.

Hydrolysis of Glucopyranosylxanthine.—Milligram quantities of the 7- and the 9-glucoside

[9] Viscontini, Hoch, and Karrer, *Helv. Chim. Acta*, 1955, **38**, 642.

were treated with N-hydrochloric acid (1 c.c.) at 100° for 1 hr., hydrolysis being followed by paper chromatography. The 9-glucoside was completely hydrolysed. The 7-glucoside also yielded xanthine and glucose, but unchanged starting material was observed. After treatment with N-acid at 100° for a further 3 hr., hydrolysis was still not quite complete.

Paper Chromatography.—Ascending chromatograms (see Table) were run on Whatman No. 4 paper in the following systems: *A*, propan-1-ol–ammonia (*d* 0·88)–water (6 : 3 : 1); *B*, the water-poor phase from butan-1-ol–acetic acid–water (4 : 1 : 5). Xanthine and the glucosylxanthines were detected by their ultraviolet absorption, or the latter by their fluorescence in ultraviolet light after exposure of chromatograms to hydrogen chloride fumes. Glucose was detected by the aniline phthalate spray.

	R_F in solvents	
	A	*B*
9-β-D-Glucopyranosylxanthine	0·34	0·17
7-Glucopyranosylxanthine	0·34	0·17
Xanthine	0·45	0·40
Glucose	0·61	0·23

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KING'S COLLEGE, UNIVERSITY OF DURHAM,
NEWCASTLE UPON TYNE, 1.

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721. *Tautomeric Pyridines. Part I. Pyrid-2- and -4-thione.*

By R. A. JONES and A. R. KATRITZKY.

Measurement of the basicities and ultraviolet spectra of 2- and 4-mercaptopyridine and their *N*- and *S*-alkyl derivatives shows that they exist in solution predominantly in the thione form.

2- and 4-AMINOPYRIDINE exist in solution predominantly as amino-compounds [1] whereas 2- and 4-hydroxypyridine exist as pyridones.[2] Published information on the mercaptopyridines is less conclusive [3-5] although *X*-ray measurements suggest that 2-mercaptopyridine exists in the crystalline state as pyrid-2-thione.[6] We have now investigated the tautomeric equilibria between the thiol and thione forms of 2- and 4-mercaptopyridine by measuring the pK_a values and ultraviolet spectra of these two compounds and of their *N*- and *S*-alkyl derivatives. The results are shown in Tables 1 and 2.

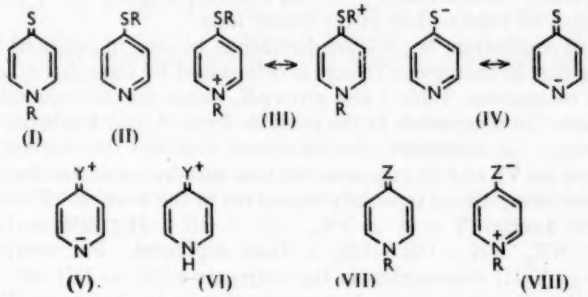
TABLE 1. pK_a *Values.*

No.	Compound	pK_a [a]	σ [b]	Concn. (10^4M)	Wavelength [c] (mμ)	pK_a of corresp. *O*-cpd.	*N*-cpd. [d]	pK_a differences *O–S*	*N–O*
1	2-Benzylthiopyridine ...	3·23 [e]	0·04	0·66	315	3·28 [g]	6·86 [h]	0·05	3·58
2	1-Methylpyrid-2-thione	−1·62	0·03	1·04	338	0·32	12·2	1·94	11·9
3	Pyrid-2-thione	−1·38	0·01	0·79	340	0·75	—	2·13	—
4		9·81	0·03	119	—	11·62	—	1·81	—
5	4-Benzylthiopyridine ...	5·41 [f]	0·06	0·54	300	6·62 [g]	9·17 [h]	1·21	2·55
6	1-Methylpyrid-4-thione	1·43	0·01	0·86	329	3·33	12·5	1·90	9·2
7	Pyrid-4-thione	1·48	0·03	0·51	324	3·27	—	1·79	—
8		8·65	0·03	177	—	11·09	—	2·34	—

[a] Arithmetical means of 6 values. Nos. 4 and 8 refer to proton loss, others to proton addition. Apparent values are given; thermodynamic pK_a may be calculated by using the concentration given (cf. ref. 2). [b] Standard deviation. [c] An entry in this column signifies that the determination was spectrometric (otherwise potentiometric). Measurements were in phosphate buffers, or sulphuric acid of known H_0, containing up to 2% ethanol. [d] From refs. 1 and 2. [e] Potentiometric titration in ethanol–water (1 : 1 v/v) gave pK_a 1·69 ± 0·02 ($5·49 \times 10^{-2}$M). [f] Potentiometric titration in ethanol–water (1 : 1 v/v) gave pK_a 4·63 ± 0·03 ($1·80 \times 10^{-2}$M). [g] These values refer to 2- and 4-methoxypyridine. [h] 2- and 4-Aminopyridine.

[1] Angyal and Angyal, *J.*, 1952, 1461.
[2] Albert and Phillips, *J.*, 1956, 1294; Mason, *J.*, 1958, 674.
[3] Ross, *J.*, 1951, 1374.
[4] Renault, *Ann. Chim.* (*France*), 1955, **10**, 135; *Bull. Soc. chim. France*, 1953, **20**, 1001.
[5] Hannen, Lieblich, and Renfrew, *J. Amer. Chem. Soc.*, 1949, **71**, 3733.
[6] Penfold, *Acta Cryst.*, 1953, **6**, 707.

On the reasonable assumption that the basicities of the individual tautomers (*e.g.*, I and II; R = H) are not greatly affected by *N*- or *S*-alkylation, the pK_a values in Table 1 indicate that 2- and 4-mercaptopyridine exist essentially as pyrid-2- and -4-thione; the thione forms are preferred by factors of *ca.* $10^{4.5}$ and *ca.* 10^4 in the 2- and the 4-series



respectively. In agreement with this view, 2- and 4-mercaptopyridine as neutral species have absorption spectra similar to those of their *N*- and quite different from those of their *S*-alkyl derivatives (Table 2). In each series, all the cations show similar ultraviolet spectra since both structures (*e.g.*, I and II) give similar mesomeric cations (*e.g.*, III); *S*-alkylation causes a bathochromic shift of *ca.* 15 mμ but *N*-alkylation has little effect.

TABLE 2. *Ultraviolet spectra.*

		Ions [a]							
		$\lambda_{min.}$		$\lambda_{max.}$		$\lambda_{min.}$		$\lambda_{max.}$	
No.		mμ	$10^{-3}\varepsilon$	mμ	$10^{-3}\varepsilon$	mμ	$10^{-3}\varepsilon$	mμ	$10^{-3}\varepsilon$
1	2-Benzylthiopyridine	234	5·6	250	8·3	276	2·7	315	9·3
2	1-Methylpyrid-2-thione	220	5·0	239	8·2	258	1·8	299	12·0
3, 4	Pyrid-2-thione	216	2·9	238	6·9	258	1·3	300	9·8
		222	6·4	262	12·8	288	4·5	308	5·6
5	4-Benzylthiopyridine	—	—	226 *	10·3	246	1·9	298	20·5
6	1-Methylpyrid-4-thione	206	4·0	222	9·9	240	1·4	286	21·6
7, 8	Pyrid-4-thione	205	3·1	222	11·3	238	0·6	282	25·1
		—	—	221	9·4	248	3·0	284	13·8

		Neutral molecules [b]							
		$\lambda_{min.}$		$\lambda_{max.}$		$\lambda_{min.}$		$\lambda_{max.}$	
No.		mμ	$10^{-3}\varepsilon$	mμ	$10^{-3}\varepsilon$	mμ	$10^{-3}\varepsilon$	mμ	$10^{-3}\varepsilon$
1	2-Benzylthiopyridine	230	6·8	248	8·3	269	3·3	290	5·5
2	1-Methylpyrid-2-thione	242	2·4	272	10·6	296	3·0	338	8·3
3, 6	Pyrid-2-thione	241	3·2	271	12·0	296	2·8	340	8·7
5	4-Benzylthiopyridine	—	—	—	—	237	4·0	265	12·2
6	1-Methylpyrid-4-thione	—	—	231	9·6	248	1·3	329	25·4
7, 8	Pyrid-4-thione	—	—	230	9·9	247	1·5	324	23·6

Solutions were aqueous, and phosphate buffers were used. * Indicates inflection.
[a] Nos. 1 and 5 in N-sulphuric acid; Nos. 2, 3, 6, 7 in 20N-sulphuric acid; nos. 4 and 8 in 0·1N-sodium hydroxide. [b] Nos. 1, 2, and 5 at pH 9·7; no. 3 at pH 3·1; no. 6 in N-sodium hydroxide; no. 7 at pH 4·8.

The anions (*e.g.*, IV) have spectra analogous to those of the corresponding cations (*e.g.*, III); presumably they have similar π-electron distributions. It is of interest that Hannen, Lieblich, and Renfrew [5] reported that the spectrum of 2-mercaptoquinoline showed a marked hypsochromic shift on passing from neutral to either acidic or basic solution; by analogy with our results this indicates that it too exists predominantly in the thione form.

Further support for our finding that 2- and 4-mercaptopyridine are properly described

as pyrid-2- and -4-thione is derived from infrared spectroscopic measurements. Of all the compounds listed in Table 2, only 2- and 4-benzylthiopyridine showed bands corresponding both to the substituent group [7] and to the 2- and the 4-substituted pyridine nucleus.[8] In their structure, therefore, the pyridine derivatives are analogous to the derivatives of pyrimidine,[9] purine,[10] and acridine [11] bearing a mercapto-group α or γ with respect to a ring nitrogen, which all exist mainly in the thione form.

The position of equilibrium in pyridine derivatives bearing in positions 2 or 4 a group capable of taking part in tautomeric change is determined by the relative basicities of the two forms. For comparison, Table 1 also gives pK_a values for corresponding oxygen and nitrogen analogues. In compounds in the pyridine form, 2- and 4-substituents affect the basicity in two ways: (*a*) mesomeric electron-release stabilises the conjugate acid (as VI) more than the base (as V), and (*b*) inductive electron-withdrawal destabilises the conjugate acid more than the base; this is especially important in the 2-series. The observed order of basicities in the 4-series ($Y = O^- > NR_2 > S^- > OR > H > SR$) and in the 2-series ($Y = O^- > S^- > NR_2 > H > OR \sim SR$) is thus explained. For compounds of the pyridone type (*e.g.*, VIII) mesomerism in the conjugate acids (as III) will be favoured in the order $Z = NR > O > S$ as above, but mesomerism in the free bases (VII—VIII) will be favoured in the order $Z = NR \ll O \sim S$ because oxygen is more electronegative, and sulphur less willing to form π-bonds, than nitrogen. This explains the observed order of basicities of compounds (VIII), $Z = NR \gg O > S$. It can now be understood that the position of equilibrium is similar in the hydroxy- and mercapto-pyridines, but different in the amino-compounds.

Experimental

Ultraviolet spectra were obtained by using a Cary model 14M-50 recording spectrophotometer, and infrared spectra by using a Perkin–Elmer model 21 instrument.

Pyrid-4-thione prepared [12] from pyrid-4-one had m. p. 184—186° (lit.,[12] m. p. 186°).

1-*Methylpyrid-4-thione*.—Pyrid-4-one [12] (1·8 g.), potassium hydroxide (0·6 g.), and methyl iodide (3·6 g.), when refluxed for 3 hr. and then evaporated, gave 1-methypyrid-4-one (1·0 g., 50%) on chloroform-extraction of the residue. The crude product (1·0 g.) [m. p. 89—90° (lit.,[13] m. p. 92—94°)] was heated with pulverised phosphorus pentasulphide (2·0 g.) for 5 hr. at 130°. The product was dissolved in hot aqueous 3N-sodium hydroxide (*ca.* 20 c.c.) and extracted with chloroform. Evaporation of the extracts gave the *thione* (0·3 g., 26%), yellow plates (from ethanol), m. p. 161—163° (Found: C, 57·7; H, 5·7. C_6H_7NS requires C, 57·6; H, 5·6%).

4-*Benzylthiopyridine*.—4-Pyridylpyridinium chloride hydrochloride [14] (10 g.) under pyridine (10 c.c.) was saturated with hydrogen sulphide, benzyl chloride (6·6 g.) was added, and the whole heated for 4 hr. at 125°. Volatile material was removed at 100°/20 mm. and the residue basified with aqueous sodium carbonate and extracted with ether. From the extracts, the *pyridine* (4 g., 45%) was obtained in plates (from ether), m. p. 61—62° (Found: C, 71·4; H, 5·5. $C_{12}H_{11}NS$ requires C, 71·6; H, 5·5%). Infrared bands due to the 2-pyridine nucleus [8] were: 3000 (50), 1584 (195), 1560 (75), (—), 1418 (200), 1280 (25), 1147 (40), {1123 (220) and 1088 (15)}, 1043 (30), 986 (30) [figures in parentheses denote ϵ_A values (cf. ref. 8)].

Pyrid-2-thione.—2-Chloropyridine (11·3 g.), thiourea (7·6 g.), and ethanol (30 c.c.) were refluxed for 1 hr., then mixed with aqueous ammonia (*d* 0·88; 15 c.c.) and kept for 5 days at 20°. Volatile material was removed at 100°/15 mm; the thione (8·0 g., 72%) (from benzene) had m. p. 124—126° (lit.,[15] m. p. 125°).

[7] Katritzky and Lagowski, *J.*, in the press.
[8] Katritzky and Gardner, *J.*, 1958, 2198; Katritzky and Hands, *J.*, 1958, 2202.
[9] Marshall and Walker, *J.*, 1951, 1004; Boarland and McOmie, *J.*, 1952, 3716.
[10] Brown and Mason, *J.*, 1957, 682.
[11] Acheson, Burstall, Jefford, and Sanson, *J.*, 1954, 3742.
[12] King and Ware, *J.*, 1939, 873.
[13] Tschitschibabin and Ossetrowa, *Ber.*, 1925, **58**, 1708.
[14] Bowden and Green, *J.*, 1954, 1795.
[15] Phillips and Shapiro, *J.*, 1942, 584.

1-Methylpyrid-2-thione, prepared [16] from 1-methylpyrid-2-one,[17] had m. p. 88—90° (lit.,[16] m. p. 89—90°).

2-Benzylthiopyridine.—Pyrid-2-thione (0·55 g.), benzyl chloride (0·63 g.), and acetone (5 c.c.) were kept for 15 hr. at room temperature. Precipitated material was taken up in 30% aqueous sodium hydroxide (5 c.c.) and extracted with chloroform. From the extracts, the *pyridine* (0·78 g., 75%), b. p. 92—94°/0·1 mm., was obtained; it solidified to needles, m. p. 28·5—29·5° (Found: N, 7·1. $C_{12}H_{11}NS$ requires N, 7·0%) (lit.,[4] oil, b. p. 153—154°/4 mm.). Infrared bands due to the 4-pyridine nucleus [8] were: 2950 (75), 1580 (300), 1540 (20), 1484 (90), 1411 (90), 1066 (35), 984 (20).

We thank Sir Alexander Todd, F.R.S., for his interest in this work. Part of this work was carried out during the tenure (by A. R. K.) of an I.C.I. Fellowship.

THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY.
THE UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, March 24th*, 1958.]

[16] Gutbier, *Ber.*, 1900, **33**, 3359.
[17] Prill and McElvain, *Org. Synth.*, 1946, Coll. Vol. 2, p. 419.

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722. *The Heats of Ionization of Ethylenediaminetetra-acetic Acid and its Dissociation as an Ammonium-ion Acid.*

By M. J. L. TILLOTSON and L. A. K. STAVELEY.

The four heats of ionization of ethylenediaminetetra-acetic acid (EDTA) have been measured calorimetrically at 20° and in solutions of ionic strength 0·1. By pH determinations with a hydrogen electrode during titration of a solution of the dipotassium salt of EDTA with acid, it has been shown that the ion H_5Y^+ exists in sufficiently acid solution, where H_4Y^0 is the neutral molecule of EDTA. pK for the stage $H_5Y^+ \longrightarrow H_4Y^0 + H^+$ has been estimated to be $1·55 \pm 0·13$, and a rough value for the associated heat content change has also been obtained. Possible structures for the various ionic species formed by EDTA are considered.

IN recent work in this laboratory [1] on the heat of formation of complexes of EDTA (ethylenediamine-*NNN'N'*-tetra-acetic acid) with metal ions, it has been necessary to know the heat content changes ΔH_3 and ΔH_4 for the ionization of the last two ionizable protons. Values of ΔH_3 and ΔH_4 have been given by Carini and Martell [2] from a careful study of the corresponding dissociation constants over a range of temperature and ionic strengths. It seemed desirable to check these values of ΔH_3 and ΔH_4 by direct calorimetric measurement. Since there is relatively little thermochemical information on polybasic acids, and in view of the interest attaching to EDTA in particular, it seemed worth while also to measure ΔH_1 and ΔH_2, *i.e.*, the heat content changes on the successive ionizaton of the first two ionizable protons, which have not yet been even indirectly determined.

These experiments involved preparing solutions of known composition and of constant ionic strength. By measuring the pH and using existing data on the four ionization constants of EDTA, the concentration of each ion in any one solution could be calculated, and it was then possible to examine the mutual consistency of all the experimental quantities involved by an electroneutrality check. So long as the pH was not too low, this check was always satisfactory, but in the experiments designed to determine ΔH_1 and ΔH_2 some of the solutions were of pH of about 2 or less, and for these there were apparently consistent departures from electroneutrality. There appeared to be an excess of negative charge amounting to as much as 4%, which could not be attributed to experimental errors. The most likely explanation of this discrepancy was that in solutions of EDTA of low pH there exist ions of the type H_5Y^+ and perhaps even H_6Y^{++} (where

[1] Care and Staveley, *J.*, 1956, 4571.
[2] Carini and Martell, *J. Amer. Chem. Soc.*, 1953, **75**, 4810.

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H_4Y^0 represents the neutral molecule of EDTA). To investigate this possibility, pH measurements were made on solutions of the dipotassium salt of EDTA during titration with a strong acid. Analysis of the results gave definite evidence of the existence of the ion H_5Y^+, and the ionization constant at 20° for the reaction $H_5Y^+ \longrightarrow H_4Y^0 + H^+$ was evaluated. A rough value for the associated heat-content change ΔH_0 was also obtained.

Experimental

EDTA was purified by dissolving it in aqueous potassium hydroxide and reprecipitating it by dilute nitric acid. After two repetitions of this process, the dry product was analyzed by titration against calcium solution, and proved to be 100·0% pure. Carbonate-free, approximately M-potassium hydroxide was prepared from silver oxide and potassium chloride. This solution, after dilution, was analyzed by titration with 0·1N-hydrochloric acid which had been standardized against a sodium carbonate solution, with which the strength of the hydrochloric acid used in the calorimetric work was also estimated.

From the solid EDTA and the ~M-potassium hydroxide, three solutions were prepared, such that the EDTA existed principally as the ions Y^{4-}, HY^{3-}, and H_2Y^{2-} respectively. The potassium content of each solution was known from the amount of potassium hydroxide used, and the total EDTA content, which was ~0·2M, was checked by titration, after dilution, against standard calcium solution. 50 ml. of one of these solutions were added to a fixed quantity (~1 l.) of a dilute solution of potassium chloride contained in the calorimeter described by Davies, Singer, and Staveley.[3] The calorimetric experiment consisted in adding to this solution, now ~0·01M in EDTA, ~20 ml. of a suitable solution of hydrochloric acid, previously contained in a double-stoppered vessel within the calorimeter, and measuring the heat change. The amount of potassium chloride present was such that the ionic strength of the solution, after addition of the acid, was 0·1. The pH of the final mixture was measured with a Cambridge pH meter after its removal from the calorimeter. (All calorimetric experiments and pH measurements were carried out at 20°.) When the EDTA was introduced essentially as K_4Y or K_3HY, the hydrochloric acid was ~0·5N. In the first case, therefore, the chief reaction occurring in the calorimeter was $Y^{4-} + H^+ \longrightarrow HY^{3-}$, and in the second $HY^{3-} + H^+ \longrightarrow H_2Y^{2-}$. With the solution of K_2H_2Y, three sets of experiments were performed, in which ~1, 2, and 3 equivalent proportions of hydrochloric acid were added, the last two necessitating the use of ~N and ~1·5N acid respectively. The relatively acid solutions resulting from these last experiments were supersaturated with respect to EDTA and sooner or later deposited it. This could readily be detected in the calorimeter from the thermal effects accompanying precipitation, but usually there was ample time to follow the " after-drift " before separation of solid occurred. (Solubility limitations made it impracticable to carry out experiments starting with K_3HY.)

Corresponding to each experiment of the type described, it was also necessary to measure the heat change when the same amount of hydrochloric acid was added to a solution of potassium chloride only, to give the same final volume (and an ionic strength of 0·1) as in the experiment with EDTA. Combination of the heat changes on dilution and reaction gave the heat change which would have been observed if the reaction had been carried out with the acid already diluted. Finally, it was necessary to prepare a replica of each ~0·01M-EDTA solution used in the calorimeter, at the concentration and ionic strength prevailing before the addition of acid, and measure its pH at 20°.

Determination of the Dissociation Constant of EDTA as an Ammonium-ion Acid.—Schwarzenbach and Ackermann [4] determined the four dissociation constants of EDTA by making pH measurements during the titration of ~0·001M-EDTA with alkali, starting at pH ~2·8. To examine the possibility of the existence of H_5Y^+ and perhaps H_6Y^{++}, at low pH values, we titrated a solution of K_2H_2Y with standard hydrochloric acid and measured the pH with a hydrogen electrode. Ideally, to correspond with the calorimetric work, the total EDTA concentration should have been ~0·01M, but precipitation would have interfered. However, three sets of experiments were carried out where EDTA concentrations were respectively ~0·001, 0·003, and 0·004M. With the most dilute solution pH values as low as 1·5 could be reached. The apparatus used had been constructed by Mr. R. Shelton and was kindly made available to us by Dr. H. M. Irving. The electrodes were platinised platinum over which

[3] Davies, Singer, and Staveley, *J.*, 1954, 2304.
[4] Schwarzenbach and Ackermann, *Helv. Chim. Acta*, 1947, **30**, 1798.

bubbled high-purity hydrogen pre-saturated with the vapour of the solution, and a silver–silver chloride electrode. To maintain a constant chloride-ion concentration, the EDTA was 0·1M in potassium chloride, and the acid (added from a microburette) was 0·1N. E.M.F. measurements were made to 0·1 mv, and pH values were calculated from the equation pH = $(E - E_0)/0{\cdot}05818$. E_0 was determined before each experiment by titrating 0·1M-potassium chloride with 0·1N-hydrochloric acid. The reliability of the electrode system was checked by frequently measuring the E.M.F. of the cell formed by immersing the hydrogen electrode in 0·1N-hydrochloric acid. This was constant at 0·3526 ± 0·0003 v throughout the work (cf. the value of 0·3525 derived from Harned and Ehlers's very careful study [5] of this system). In the EDTA titrations, the E.M.F. values recorded for a given amount of hydrochloric acid added could be reproduced from run to run to within 0·1 mv.

Results

Ionization of EDTA as an Ammonium-ion Acid.—It was first assumed that both the ions H_5Y^+ and H_6Y^{++} exist at low pH values at concentrations determined by the equations

$$K_0 = [H^+][H_4Y^0]/[H_5Y^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$K_{00} = [H^+][H_5Y^+]/[H_6Y^{++}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

K_0 and K_{00} are " concentration constants " at 20° with a constant salt background of 0·1N-potassium chloride. K_0 and K_{00} were evaluated from the pH titration data by a method similar to that employed by Schwarzenbach, Willi, and Bach.[6] At the low pH values concerned here the concentrations of the ions HY^{3-} and Y^{4-} are negligible, and the only relevant equilibria are those controlled by K_1, K_2, K_0, and K_{00}, where

$$K_1 = [H^+][H_3Y^-]/[H_4Y^0] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$K_2 = [H^+][H_2Y^{2-}]/[H_3Y^-] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The following two relations must also hold:

$$[Y] = [H_2Y^{2-}] + [H_3Y^-] + [H_4Y^0] + [H_5Y^+] + [H_6Y^{++}] \quad . \quad . \quad . \quad (5)$$

$$[H^+] + [K^+] + [H_5Y^+] + 2[H_6Y^{++}] = [Cl^-] + 2[H_2Y^{2-}] + [H_3Y^-] \quad . \quad (6)$$

[Eqn. (6) is the electroneutrality requirement.] [Y] is the total concentration of EDTA, $[K^+]$ the concentration of potassium ion associated with the EDTA, and $[Cl^-]$ the concentration of the chloride ion due to the added hydrochloric acid. [Y], $[K^+]$, and $[Cl^-]$ are all known. From eqns. (1)—(6) it follows that

$$K_0 = P(1/K_{00}) + Q \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

where $P = [H^+]^2([H^+] + [K^+] - [Cl^-] + 2[Y])/D$

and $Q = [H^+]([H^+] + [K^+] - [Cl^-] + [Y])/D$

with $$D = [Y]\left(\frac{2K_1K_2}{[H^+]^2} + \frac{K_1}{[H^+]}\right) - ([H^+] + K^+] - [Cl^-])\left(\frac{K_1K_2}{[H^+]^2} + \frac{K_1}{[H^+]} + 1\right)$$

From any one pH value, P and Q can be evaluated, and for these values of P and Q and for various arbitrary values of say, $1/K_{00}$, corresponding values of K_0 can be obtained, which give a straight line when plotted against $1/K_{00}$. Ideally, these lines (one for each of the experimental pH values) should meet at a point, the co-ordinates of which give the actual values of K_0 and $1/K_{00}$. The points of intersection, however, fell randomly on either side of the K_0 axis, implying that $1/K_{00}$ was zero and K_{00} infinite, *i.e.*, that in the pH range studied the ion H_6Y^{++} does not exist in significant amounts. On the other hand, all lines made approximately the same intercept [the Q of eqn. (7)] on the K_0 axis, and the mean value of Q was taken to be K_0. From seventeen values of Q taken from three sets of experiments, it was found that $K_0 = 2{\cdot}80 \pm 0{\cdot}75 \times 10^{-2}$, whence $pK_0 = 1{\cdot}55 \pm 0{\cdot}13$. With this value of K_0, the electroneutrality discrepancy which had prompted the investigation was removed. This is shown in Table 1, which relates to one of the runs carried out with ~0·003M-EDTA. It will be seen that without the introduction of

[5] Harned and Ehlers, *J. Amer. Chem. Soc.*, 1932, **54**, 1350.
[6] Schwarzenbach, Willi, and Bach, *Helv. Chim. Acta*, 1947, **30**, 1303.

the ion H_5Y^+ there is a persistent discrepancy between the apparent total positive and negative charges, but that with the above value of K_0 the discrepancy becomes random and small.

TABLE 1. *Specimen electroneutrality check.* $10^{-3}A = [H^+] + [K^+]$; $10^{-3}B = [Cl^-] + 2[H_2Y^{2-}] + [H_3Y^-]$; $10^{-3}C = [H^+] + [K^+] + [H_5Y^+]$. (Concns. in g.-ions/l.)

	Without H_5Y^+		With H_5Y^+			Without H_5Y^+		With H_5Y^+	
pH	$A(+)$	$B(-)$	$C(+)$	$B(-)$	pH	$A(+)$	$B(-)$	$C(+)$	$B(-)$
2·011	14·84	15·44	15·18	15·22	1·678	25·40	26·43	26·12	26·16
1·908	17·28	18·02	17·73	17·76	1·629	27·72	28·74	28·49	28·48
1·807	20·34	21·08	20·91	20·82	1·592	29·73	30·92	30·52	30·67
1·731	23·13	23·98	23·79	23·71					

Heats of Ionization.—The experimental results are shown in Table 2 with the change in ionic composition in each experiment, since these changes are relevant to a consideration of the relative accuracies of the individual heat of ionization values. Each value for the heat evolved is the mean of two concordant figures, and should be accurate to $\pm 0{\cdot}5$ cal. A substantial contribution to the heat change in the first experiment comes from the neutralization of hydroxyl ions, for which process a heat content change of $-13{,}800$ cal./g.-ion was taken.[7] The hydroxyl-ion concentration of the solution before the addition of acid was calculated by using a K_w value of $1{\cdot}02 \times 10^{-14}$, which was determined by experiments at 20° on standard potassium hydroxide solutions ($\sim 10^{-3}$M) of the appropriate ionic strength, with the same glass electrode as was employed in the pH measurements in the calorimetric work.

Each of the five measured heat quantities recorded in Table 2 can be expressed in terms of two or more of the heat content changes ΔH_0 to ΔH_4. Thus, the heat evolved in reaction 1 (Table 2) can be expressed in terms of ΔH_3 and ΔH_4, that in reaction 2 in terms of ΔH_2, ΔH_3, and ΔH_4, and so on.

TABLE 2. *Amounts of the various ionic species in* 10^{-3} *g.-ions in the calorimeter before and after the addition of acid, and the mean value in calories of the heat evolved on the addition of acid.* Temp., 20°; final ionic strength, 0·1; total EDTA concn., $\sim 10^{-2}$M; 1 cal. = 4·1840 abs. joules.

Approx. reaction		OH^-	Y^{4-}	HY^{3-}	H_2Y^{2-}	H_3Y^-	H_4Y^0	H_5Y^+	Heat evolved
1) $K_4Y + HCl$	Before	1·33	7·75	1·32	—	—	—	—	—
	After	—	0·01	8·58	0·47	—	—	—	+64·44
(2) $K_3HY + HCl$ ...	Before	—	0·12	9·34	0·05	—	—	—	—
	After	—	—	0·24	9·17	0·10	—	—	+41·03
(3) $K_2H_2Y + HCl$...	Before	—	—	0·56	8·75	0·04	—	—	—
	After	—	—	—	3·81	4·37	1·07	0·10	−5·64
(4) $K_2H_2Y + 2HCl$	Before	—	—	0·64	8·69	0·04	—	—	—
	After	—	—	—	1·37	4·35	2·94	0·71	−9·55
(5) $K_2H_2Y + 3HCl$	Before	—	—	0·56	8·75	0·04	—	—	—
	After	—	—	—	0·53	3·13	3·93	1·76	−11·92

The five heat content changes ΔH_0 to ΔH_4 were thus calculated from the results of Table 2 by solving the five simultaneous equations. It will be clear that the relative accuracies of these quantities vary widely. The most accurate are, of course, ΔH_3 and ΔH_4. Experiment 2 (Table 2), in particular, depends more nearly than any other on one process only, namely $H^+ + HY^{3-} \longrightarrow H_2Y^{2-}$, and so should give a good value for ΔH_3. ΔH_3 and ΔH_4 should be accurate within ~1%. The only values for comparison are those derived by Carini and Martell [2] from the temperature variation of K_3 and K_4, which are $\Delta H_3 = 3690$ and $\Delta H_4 = 5340$ cal./g.-ion. With regard to the discrepancies between our values and theirs, it is recognized that heat content changes derived, as were Carini and Martell's, by the temperature-coefficient method can seldom be as accurate as those measured directly (see, *e.g.*, Rowlinson [8]). In experiment 3 (Table 2), about half of the EDTA has undergone the conversion $H^+ + H_2Y^{2-} \longrightarrow H_3Y^-$, and though some H_4Y^0 has been formed, ΔH_1 is undoubtedly small and so most of the observed heat change is due to the formation of H_3Y^- from H_2Y^{2-}. The resulting value for

[7] Harned and Owen, "Physical Chemistry of Electrolytic Solutions," Reinhold Publ. Corpn., New York, 2nd Edn., 1950, p. 494.

[8] Rowlinson, *Discuss. Faraday Soc.*, 1957, **24**, 121.

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ΔH_2 should therefore be fairly reliable. Least accurate of all are ΔH_0 and ΔH_1, and perhaps it would be unwise to claim more for the values presented than that they show that these two quantities are numerically small and do not differ much from each other.

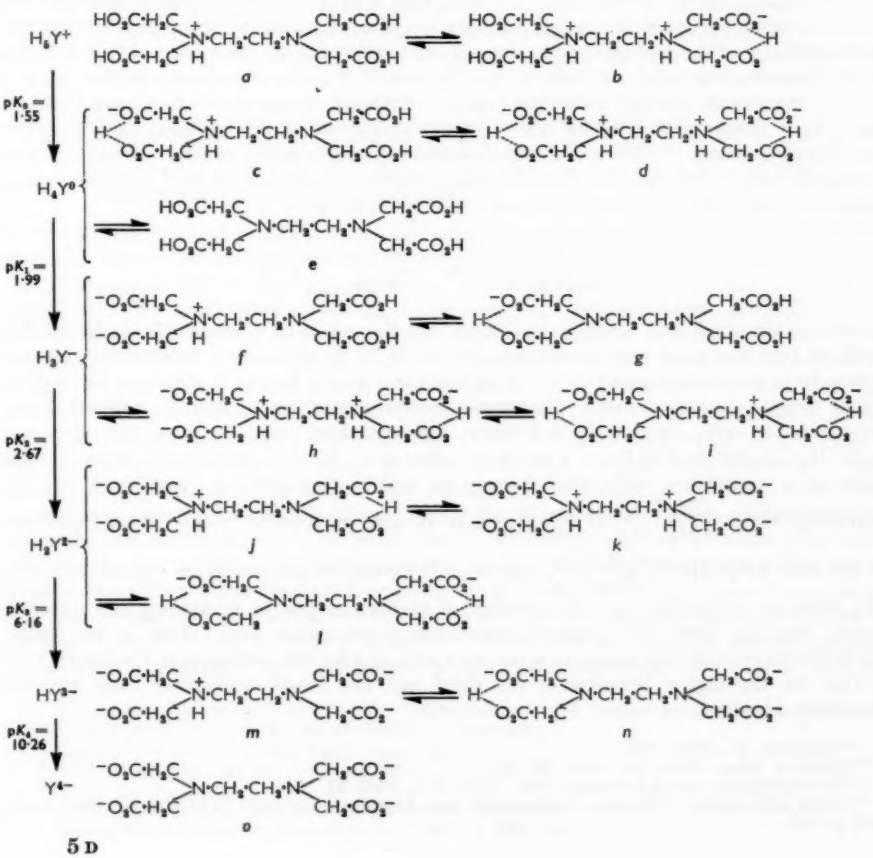
Discussion

The values of ΔG, ΔH, and ΔS for the five ionization processes are recorded in Table 3. The values of pK_1 to pK_4 are those given by Schwarzenbach and Ackermann.[4] Although

Table 3. *Thermodynamic parameters for the various ionization stages of* EDTA *at* 20°. *ΔG and ΔH in cal./mole, ΔS in cal./mole deg.*

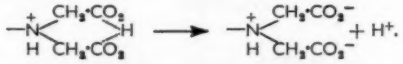
Reaction	pK	ΔG	ΔH	ΔS
$H_5Y^+ \longrightarrow H_4Y^0 + H^+$	1·55	2,080	−490	−8·8
$H_4Y^0 \longrightarrow H_3Y^- + H^+$	1·99	2,680	−180	−9·8
$H_3Y^- \longrightarrow H_2Y^{2-} + H^+$	2·67	3,580	−1,430	−17·1
$H_2Y^{2-} \longrightarrow HY^{3-} + H^+$	6·16	8,260	+4,390	−13·2
$HY^{3-} \longrightarrow Y^{4-} + H^+$	10·26	13,760	+5,690	−27·5

information on ΔH for simpler polycarboxylic acids and amino-acids is rather meagre, the thermodynamic parameters of Table 3 should throw some light on the structures of the various ions formed by EDTA. The various possibilities for these structures are shown in the annexed ionization scheme.



In attempting to decide which structures are the most probable, the following points should be noted: (1) It is highly likely that for some ions, at least, there is tautomeric equilibrium between two or more structures. If equilibrium prevails between two tautomers HA and HB, the apparent ionization constant will fall between the values for the two separate structures. (2) From a study of the infrared spectrum of the disodium salt of EDTA, Chapman [9] concluded that, in the solid salt at least, the ion H_2Y^{2-} does not have the double zwitterion structure in which both nitrogen atoms are linked to protons. In view of this and of our own finding that the value of K_{00} (eqn. 2) seems to be effectively zero, it is unlikely that structures such as *b*, *d*, and *h* are important. Chapman's work, however, does not seem to be inconsistent with the possibility of the existence of single betaine structures, and our demonstration of the probable existence of H^5Y^+ requires that, in solution at least, such structures must be considered in any ionization scheme. (3) As Chapman pointed out, structures such as *c* and *j* which contain the group $-N<^{CH_2\cdot CO_2^-}_{CH_2\cdot CO_2H}$ should be somewhat stabilized by internal hydrogen-bond formation between the OH and CO_2^- groups. This stabilization no doubt results primarily from favourable entropy factors.[10]

With these considerations in mind, *a* and *c* seem the most probable structures for the species H_5Y^+ and H_4Y^0 respectively. We should expect pK_0 to be appreciably less than the corresponding figure of 2·35 for the protonated form of glycine, just as pK_1 for glutaric acid is less than pK for acetic acid. It might appear that the next proton is lost from the carboxyl group adjacent to the carboxylate ion, *i.e.*, from the charged rather than the uncharged end of the molecule, since the pK_1 of 1·996 is not far from the value of 2·12 for methyliminodiacetic acid. However, for the ion H_3Y^-, the structure *i* rather than *f* may be dominant, for the following reason. Schwarzenbach and Ackermann [11] found that pK_2 is almost unaffected by increasing the number of methylene groups between the two nitrogen atoms. With a sufficient number of such groups, there is no reason why the double zwitterion structure should not be preferred, and both the first and the second ionization stage (starting from H_4Y^0) will then be as follows:



In view of the constancy of pK_2, it is likely that this mode of ionization holds for EDTA itself, so that the most important structure for H_3Y^- is probably *i*, formed by loss of a proton from a carboxyl group of *c*. This leads to *j* as the favoured structure for H_2Y^{2-}, which seems consistent with Chapman's spectroscopic work and is supported by the value of pK_3, which is not very different from pK_1 (= 5·58) for the acid $H_2N\cdot CH_2\cdot CH_2\cdot N(CH_2\cdot CO_2H)_2$. This last substance in its uncharged form should exist as a zwitterion with the charges as widely separated as possible,[12] *i.e.*, as $H_3\overset{+}{N}\cdot CH_2\cdot CH_2\cdot N<^{CH_2\cdot CO_2^-}_{CH_2\cdot CO_2H}$ (cf. structure *j*), and on losing a proton should produce an ion $H_3\overset{+}{N}\cdot CH_2\cdot CH_2\cdot N<^{CH_2\cdot CO_2^-}_{CH_2\cdot CO_2^-}$ (cf. *m*). It should be noted that, in contrast to pK_2, pK_3 increases markedly with the number of methylene groups separating the nitrogen atoms, reaching 9·94 for octamethylenediaminetetra-acetic acid. This is no doubt due to the increasing importance of structures such as *k* for the analogues of the ion H_2Y^{2-}, so that for the higher homologues the third and the fourth ionization stage become essentially identical.

[9] Chapman, *J.*, 1955, 1766.
[10] Jaffe, *J. Amer. Chem. Soc.*, 1957, **79**, 2373.
[11] Schwarzenbach and Ackermann, *Helv. Chim. Acta*, 1948, **31**, 1029.
[12] Cohn and Edsall, "Proteins, Amino-acids, and Peptides," Reinhold Publ. Corpn., New York, 1943, p. 103.

As regards the last ionization stage, ΔH for the second ionization of a simple mono-amino-monocarboxylic acid is usually between 10,000 and 11,000 cal., while for the trimethylammonium ion ΔH is 8500 cal. ΔH_4 for EDTA is considerably smaller than these figures. Moreover, ΔS_4 differs considerably from the value of $\sim$—8 e.u. associated with the second ionization stage of an acid like glycine. It is therefore difficult to believe that the fourth ionization stage is simply represented by $m \longrightarrow o$. Rather would it appear that a significant proportion of the ions HY^{3-} have the structure *n*. If *m* and *n* compete on comparable terms, the possible participation of structures such as *l* and *g* cannot be disregarded.

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723. *The Frequencies and Intensities of the* N–H *Stretching Vibrations in Primary Amines.*

By S. F. MASON.

The positions, extinction coefficients, and band half-widths of the symmetric and antisymmetric stretching vibration absorptions of the amide anion, and some monocyclic aliphatic, aromatic, and *N*-heteroaromatic primary amides have been measured in the 3 μ region. Approximate values for the force constants, H–N–H bond angles, the "*s*" character of the hybrid orbitals bonding nitrogen to hydrogen, and the N–H bond dipole gradients have been calculated from the results. It is found that the force constant and the N–H bond dipole gradient increase linearly with the amount of "*s*" character of the hybrid orbitals of the N–H group, and that, in the aromatic series, these quantities increase as the π-electron charge density on the nitrogen atom of the amino-group falls.

IT is well known [1] that the mechanical and electrical properties of C–H bonds vary widely with the type of hybridisation of the carbon atom orbital, and there are indications that the properties of N–H bonds vary similarly. It has been observed that the H–N–H bond angle [2] and the N–H bond stretching force constant [3] in substituted aromatic amines increase with the electron-attracting power of the substituents, and more recently it has been found [4,5] that the frequencies and the intensities of the fundamental stretching vibration absorptions of the primary amino-group in substituted anilines are smooth functions of the Hammett σ constant of the substituent. In the present work a survey has been made of the positions and intensities of the symmetric and antisymmetric stretching vibration bands of a wide range of primary amines, varying from the amide anion, through *cyclo*hexylamine and aniline, to 3-amino-1 : 2 : 4-triazine, in order to obtain more extensive and more quantitative information of the effect of hybridisation and conjugation upon the mechanical and electrical properties of the N–H group. In the series of aromatic amines a single "substituent," * the aza-nitrogen atom, was employed as far as possible, so that the effect of substituents upon the π-electron charge density of the amino-nitrogen atom could be calculated quantitatively in terms of a single semi-empirical constant common to the series, the Coulomb integral of nitrogen. The use of ring-nitrogen substituents had the further advantage that conjugation in the *ortho*-"substituted" amines was not

* Throughout this paper, "substituted," "substitution," and "substituent" refer to *replacement* of a CH-member of the benzene ring, specifically by nitrogen.

[1] Coulson, "Valence," Oxford Univ. Press, 1952.
[2] Flett, *Trans. Faraday Soc.*, 1948, **44**, 767.
[3] Short, *J.*, 1952, 4584.
[4] Califano and Moccia, *Gazzetta*, 1956, **86**, 1014; 1957, **87**, 58.
[5] Krueger and Thompson, *Proc. Roy. Soc.*, 1957, *A*, **243**, 143.

hindered sterically. The observed positions, maximum extinction coefficients, and band widths at half-maximum extinction of the amino-group stretching vibrations in the compounds studied are recorded in Tables 1 and 2.

TABLE 1. *The positions of the symmetric* (ν_s) *and antisymmetric* (ν_a) *stretching vibrations of the amino-group in the amide anion, and some monocyclic aliphatic and aromatic primary amines. The* N–H *stretching vibration force constants* (k), *the* H–N–H *bond angles* (θ), *the " s " character of the nitrogen hybrid orbitals of the* N–H *bonds expressed as the coefficient* (b), *where* $\psi_{hybrid} = b\psi_s + \sqrt{(1 - b^2)} \cdot \psi_p$, *and the* π*-electron charge density on the nitrogen atom of the amino-group* (q_N).

No.	Compound	Solvent	ν_s (cm.$^{-1}$)	ν_a (cm.$^{-1}$)	10^5k [b] (dyne cm.$^{-1}$)	θ [b]	b [c]	q_N [d] (electrons)
1	Lithium amide	[a]	3315	3261	5·99	104·1°	0·436	—
2	*cyclo*Hexylamine	CCl_4	3381	3316	6·21	106·8	0·473	—
3	Aniline	,,	3481	3395	6·54	111·8	0·519	1·802
4	2-Aminopyridine	,,	3509	3410	6·62	115·3	0·547	1·742
5	2-Aminopyridine	$CHCl_3$	3512	3408	6·62	116·5	0·557	—
6	3-Aminopyridine	CCl_4	3481	3396	6·54	111·6	0·518	1·774
7	3-Aminopyridine	$CHCl_3$	3484	3400	6·56	111·3	0·516	—
8	4-Aminopyridine	CCl_4	3505	3413	6·62	113·5	0·535	1·730
9	4-Aminopyridine	$CHCl_3$	3512	3415	6·64	114·7	0·544	—
10	2-Aminopyrimidine	CCl_4	3540	3425	6·72	119·3	0·573	1·682
11	2-Amino-4 : 6-dimethylpyrimidine	$CHCl_3$	3533	3422	6·69	118·5	0·567	—
12	4-Aminopyrimidine	CCl_4	3536	3421	6·70	119·3	0·573	1·658
13	5-Aminopyrimidine	,,	3485	3399	6·56	111·8	0·520	1·745
14	5-Aminopyrimidine	$CHCl_3$	3488	3403	6·57	111·6	0·519	—
15	2-Aminopyrazine	CCl_4	3511	3410	6·62	115·8	0·551	1·714
16	2-Aminopyrazine	$CHCl_3$	3515	3410	6·64	116·8	0·558	—
17	3-Amino-6-methylpyridazine	,,	3509	3407	6·62	116·1	0·553	1·724
18	4-Aminopyridazine	,,	3514	3415	6·64	115·3	0·548	1·717
19	3-Amino-1 : 2 : 4-triazine	,,	3353	3420	6·70	119·0	0·572	1·664
20	3-Amino-5 : 6-dimethyl-1 : 2 : 4-triazine	CCl_4	3534	3423	6·68	118·5	0·569	—

[a] Solid in a potassium bromide disc: quoted from Mason, *J. Phys. Chem.*, 1957, **61**, 384. [b] Calc. by eqns. (1) and (2). [c] Calc. by eqn. (4). [d] Calc. by eqn. (5) with $\Delta\alpha_C = 0{\cdot}2\Delta\alpha_N$ and $\Delta\alpha_N = 0{\cdot}6\beta$.

I. *Frequencies.*—In the present work it is assumed that the two absorption bands in the 3200—3550 cm.$^{-1}$ region of the infrared spectra of primary amines are due to vibrations in which only the nitrogen and hydrogen atoms of the amino-group move. It is assumed further that the nitrogen and hydrogen atoms vibrate along the N–H bond directions, the stretching force constant being much larger than the deformation and interaction constants. In general, these assumptions are reasonable [6] for the vibrations of bonds to hydrogen atoms, and in the present case they are justified empirically, as a more exact treatment has shown [7] that the N–H stretching force constant is an order of magnitude larger than the deformation and interaction constants in the ammonia molecule. With these assumptions the H–N–H bond angle (θ) and the N–H stretching force constant (k) may be calculated from the frequencies of the symmetric (ν_s) and the antisymmetric (ν_a) absorption bands of a primary amine by using the valency force field equations given by Linnett,[6] namely:

$$4\pi^2\nu_s^2 = k[1/m_H + (1 + \cos\theta)/m_N] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$4\pi^2\nu_a^2 = k[1/m_H + (1 - \cos\theta)/m_N] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where m_H and m_N are the mass of the hydrogen and the nitrogen atom respectively.

The bond angles and force constants of the primary amines studied, calculated by means of equations (1) and (2), are recorded in Table 1. Owing to the approximations used, no

[6] Linnett, *Trans. Faraday Soc.*, 1945, **41**, 223.
[7] McKean and Schatz, *J. Chem. Phys.*, 1956, **24**, 316.

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claim can be made for the accuracy of the absolute values of the calculated bond angles and force constants, though it is probable that the relative values in the series of amines are reliable. The calculated bond angles are, however, acceptable. That of the amide ion (104·1°) is close to the bond angle of the isoelectronic molecule, water [8] (104·22°); that of *cyclo*hexylamine (106·8°) close to that of ammonia [8] (106·78°); and in the aromatic series the calculated angles increase with conjugation between the nucleus and the amino-group nearly up to the maximum value of 120° which is to be expected when the lone-pair electrons of the amino-group are fully delocalised over the aromatic nucleus (Table 1).

From the H–N–H bond angles of the primary amines the contribution of the 2*s* and the 2*p* atomic orbitals of the nitrogen atom to the hybrid orbitals binding the hydrogen atoms

TABLE 2. *The maximum extinction coefficients,* $E = (1/cl) \log (T_0/T)\ \nu_{max.}$, *and the band half-widths* ($\Delta\nu_{\frac{1}{2}}$) *of the amino-group stretching vibrations in the amide ion and some monocyclic aliphatic, aromatic, and* N*-heteroaromatic amines. The apparent* H–N–H *bond angle* (α), *and the* N–H *bond moment gradient derived from the intensities of the symmetric* $(dM/dr)_s$ *and the antisymmetric* $(dM/dr)_a$ *stretching vibration bands.*

			Antisymmetric			Symmetric			
No.	Compound	Solvent	E (l. mole^{-1} cm.$^{-1}$)	$\Delta\nu_{\frac{1}{2}}$ (cm.$^{-1}$)	$(dM/dr)_a$ [b] (D/Å)	E (l. mole^{-1} cm.$^{-1}$)	$\Delta\nu_{\frac{1}{2}}$ (cm.$^{-1}$)	$(dM/dr)_s$ [c] (D/Å)	α [d]
1	Lithium amide	[a]	6·5	10	0·2	17·7	14	0·6	55°
2	*cyclo*Hexylamine	CCl_4	3·3	37	0·3	2·2	55	0·4	90
3	Aniline	,,	20	36	0·6	28	25	1·0	91
4	2-Aminopyridine	,,	44	34	0·9	66	23	1·5	90
5	2-Aminopyridine	$CHCl_3$	45	43	1·0	61	34	1·8	88
6	3-Aminopyridine	CCl_4	30	34	0·7	43	24	1·2	90
7	3-Aminopyridine	$CHCl_3$	32	40	0·8	47	28	1·3	89
8	4-Aminopyridine	CCl_4	41	34	0·9	67	23	1·4	87
9	4-Aminopyridine	$CHCl_3$	46	40	1·0	78	27	1·7	85
10	2-Aminopyrimidine	CCl_4	80	32	1·1	114	22	2·0	91
11	2-Amino-4 : 6-dimethyl-pyrimidine	$CHCl_3$	80	37	1·2	105	26	2·1	92
12	4-Aminopyrimidine	CCl_4	75	32	1·1	122	22	2·0	87
13	5-Aminopyrimidine	,,	39	33	0·9	56	24	1·3	89
14	5-Aminopyrimidine	$CHCl_3$	34	42	0·9	58	32	1·6	83
15	2-Aminopyrazine	CCl_4	57	33	1·0	89	23	1·8	88
16	2-Aminopyrazine	$CHCl_3$	66	41	1·2	90	31	2·1	88
17	3-Amino-6-methyl-pyridazine	,,	54	40	1·1	73	31	1·8	90
18	4-Aminopyridazine	,,	50	39	1·0	88	27	1·8	84
19	3-Amino-1 : 2 : 4-triazine	,,	108	36	1·4	149	24	2·4	92
20	3-Amino-5 : 6-dimethyl-1 : 2 : 4-triazine	CCl_4	91	32	1·2	134	22	2·2	90

[a] See Table 1. [b] Calc. according to eqns. (7), (9), and (11). [c] Calc. according to eqns. (7), (8) and (11). [d] Calc. according to eqns. (10) and (11).

may be derived. The values for the " *s* " character of the nitrogen orbitals are listed in Table 1 as the coefficient (b) of the 2*s*-orbital of nitrogen in the hybrid,

$$\psi_{hybrid} = b\psi_{2s} + \sqrt{(1 - b^2)} \cdot \psi_{2p} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

If the two N–H bonds of a given primary amino-group are equivalent, and the hybrid orbitals of nitrogen binding the two hydrogen atoms are orthogonal, the coefficient (b) is related to the H–N–H bond angle by the expression:

$$b^2 = -\cos\theta/(1 - \cos\theta) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The π-electron charge density upon the nitrogen atom of the amino-group (q_N) of the aromatic and *N*-heteroaromatic amines given in Table 1 was obtained from the charge

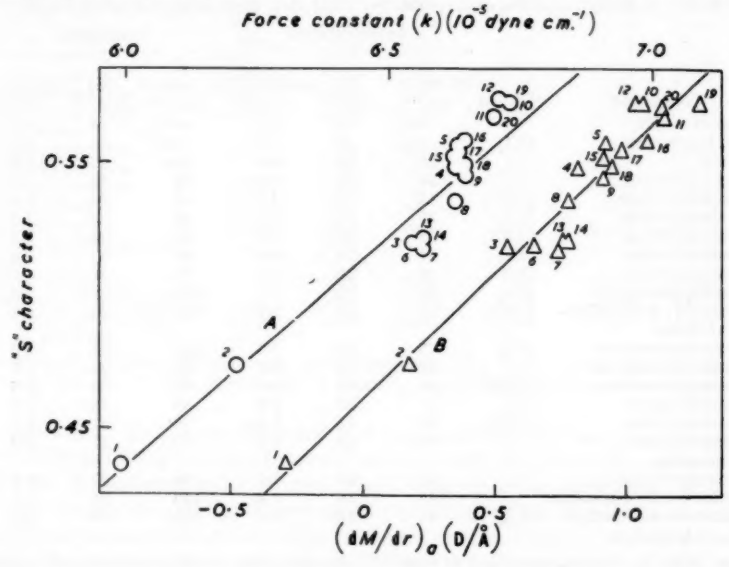
[8] Herzberg, " Infrared and Raman Spectra of Polyatomic Molecules," Van Nostrand, New York, 1945.

density on the exocyclic atom [9] (q_r), and the atom–atom polarisabilities [10] of the benzyl anion according to the expression:

$$q_N = q_r + \sum \pi_{N \cdot N'} \Delta\alpha_N + \sum \pi_{C \cdot N'} \Delta\alpha_C \quad . \quad . \quad . \quad . \quad . \quad (5)$$

where $\pi_{N \cdot N'}$ refers to the mutual polarisability of two positions occupied by nitrogen atoms, one of which, N′, is the nitrogen atom of the amino-group, the sum being taken over all nitrogen atoms in the molecule including the case where N = N′, and $\pi_{C \cdot N'}$ refers to the mutual polarisability of a position occupied by a carbon atom (C) adjacent to a nuclear nitrogen atom, and the position occupied by the exocyclic nitrogen atom (N′). $\Delta\alpha_N$ is the difference between the Coulomb integrals of the carbon and the nitrogen atom, and $\Delta\alpha_C$ the increment in the Coulomb integral of a carbon atom adjacent to a nitrogen atom.

FIG. 1. *Relations between the " s " character of the hybrid orbitals bonding the hydrogen atoms to the nitrogen atom of the amino-group, expressed as the coefficient (b) in equation (6), and (A) the N–H stretching vibration force constant (k), and (B) the N–H bond dipole gradient* $(dM/dr)_e$. *The numbers refer to the compounds listed in Tables 1 and 2.*



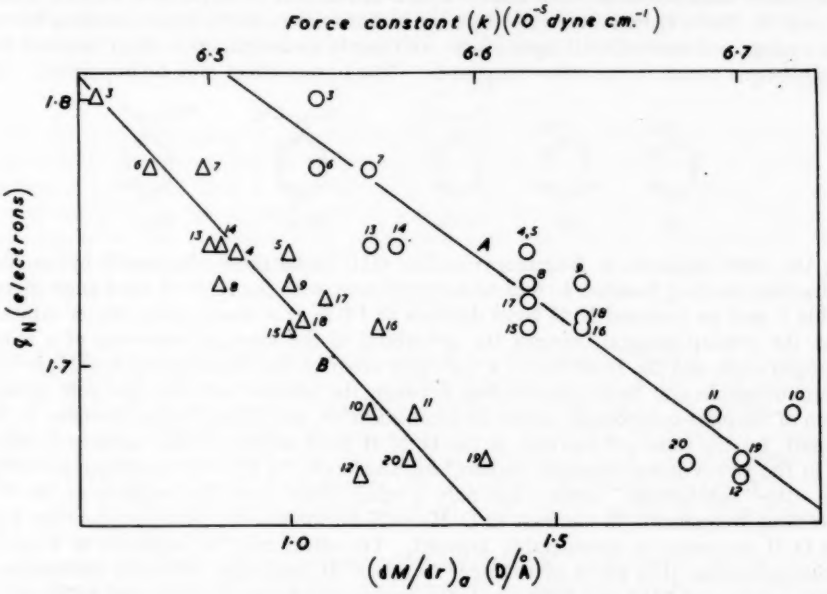
$\Delta\alpha_C$, which is a measure of the inductive enhancement of the electronegativity of a carbon atom by an adjacent nitrogen atom, is related to $\Delta\alpha_N$. Empirically it has been shown [11] that $\Delta\alpha_C = 0{\cdot}2\Delta\alpha_N$, and a variety of evidence suggests [11] that $\Delta\alpha_N = 0{\cdot}6\beta$, where β is the carbon–carbon resonance integral. These values were adopted in calculating, by equation (5), the values of q_N given in Table 1.

From the quantities listed in Table 1, it is found (Fig. 1*A*) that the N–H stretching vibration force constants (k) of the primary amines studied increase with the " *s* " character of the hybrid bonds from nitrogen to hydrogen, expressed as the coefficient (b) of equation (3). Such a correlation does not conform to the measure of *sp* hybrid-bond strength proposed by Pauling and Sherman,[12] which is known to be unsatisfactory for hybrid bonds between carbon and hydrogen.[1] According to Pauling and Sherman,[12] *sp*

[9] Longuet-Higgins, *J. Chem. Phys.*, 1950, **18**, 265.
[10] Jaffe, *J. Amer. Chem. Soc.*, 1954, **76**, 3527.
[11] Mason, *J.*, 1958, 674.
[12] Pauling and Sherman, *J. Amer. Chem. Soc.*, 1937, **59**, 1450.

hybrid bonds from a given atom have a maximum strength at tetrahedral hybridisation when, in the present terminology, $b = 0{\cdot}5$, but the force constant of the N–H bond shows no maximum in the range ($b = 0{\cdot}44$—$0{\cdot}57$) covered in the present work (Fig. 1*A*). A more satisfactory measure of bond strength is provided by the overlap integral [1] of the hybrid orbital of the nitrogen atom with the 1*s* orbital of the hydrogen atom. By assuming a constant N–H bond distance of 1·0 Å in the range of amines covered, it is found, using Slater orbitals,[13] that the overlap integrals of the 2*s*- and the 2*p*-orbitals of nitrogen with

FIG. 2. *Relations between the π-electron charge density on the nitrogen atom of the amino-group (q_N) and (A) the N–H stretching vibration force constant (k), and (B) the N–H bond moment gradient (dM/dr_a), in the series of aromatic amines. The numbers refer to the compounds listed in Tables 1 and 2.*



the 1*s* orbital of hydrogen are 0·55 and 0·42 respectively. Thus the overlap integral (S) for a hybrid orbital of nitrogen, given by equation (3), and a 1*s* orbital of hydrogen is:

$$S = 0{\cdot}55b + 0{\cdot}42\sqrt{(1 - b^2)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

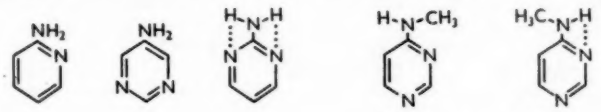
The overlap integral (S), given by equation (6), has a maximum value when $b = 0{\cdot}79$, that is, when the N–H bond has slightly more than digonal "*s*" character. Over the range covered in the present work ($b = 0{\cdot}44$—$0{\cdot}57$), the overlap integral (S) increases approximately linearly with b, in accord with the observed increase in the force constant (k) with the "*s*" character (b) of the N–H bonds (Fig. 1*A*).

In the series of aromatic amines the N–H stretching vibration force constant (k) increases as the π-electron charge density (q_N) on the amino-nitrogen atom falls (Fig. 2*A*). The decrease of charge density (q_N) may be expected to have two effects upon the N–H bonds of the amino-group. First, the lone-pair orbital of the nitrogen atom of the amino-group should become more purely $2p\pi$ as the non-bonding electrons are increasingly delocalised over the aromatic nucleus, so that the N–H bonds attain an increased "*s*" character and become stronger. Secondly, the electronegativity of the nitrogen atom of

[13] Mulliken, Rieke, Orloff, and Orloff, *J. Chem. Phys.*, 1949, **17**, 1248.

the amino-group increases as the charge density (q_N) falls, so that the hydrogen atoms are bound more firmly. The two effects may be distinguished, for the N–H bonds have the same " *s* " character in aniline and in 5-aminopyrimidine, yet the force constant of the latter is larger than that of the former, corresponding to a fall in the charge density (q_N). Moreover, *ortho*-" substitution " with a single nitrogen atom results in a large increase in the " *s* " character of the N–H bonds, whilst two *meta*-nitrogen " substituents " result in no increase, though the charge densities (q_N) in 2-aminopyridine (I) and 5-aminopyrimidine (II) are closely similar (Table 1).

In general, ring-nitrogen " substituents " in aniline increase the H–N–H bond angle and the " *s* " character of the N–H bonds in the order, *ortho* > *para* > *meta* (Table 1). The greater influence of an *ortho*- than of a *para*-substituent (compare Nos. 4 and 8, 5 and 9, 17 and 18, Table 1) may be ascribed partly to intramolecular hydrogen-bonding between the nuclear and exocyclic nitrogen atoms, and partly to an inductive effect between these two nitrogen atoms in the *ortho*-compounds. The former effect may be important. Tak-



(I) (II) (III) (IVa) (IVb)

ing the bond distances in 2-aminopyrimidine (III) to be those obtained [14] by an *X*-ray diffraction study of 2-amino-4 : 6-dichloropyrimidine, with the H–N–H bond angle given in Table 1, and an assumed N–H bond distance of 1·0 Å, it is found, using Slater orbitals,[13] that the overlap integral between the sp^2-orbital of the lone-pair electrons of a nuclear nitrogen atom and the 1*s*-orbital of a hydrogen atom of the amino-group in (III) is 0·077. Thus intramolecular hydrogen-bonding between the nuclear and the exocyclic nitrogen atom of the *ortho*-compounds cannot be inconsiderable, and it must be responsible, at least in part, for the observed increase in the H–N–H bond angles of these amines (Table 1). As in the *peri-N*-heteroaromatic amines,[3] intramolecular N–H · · · N hydrogen-bonding in the *ortho*-" substituted " amines has only a small effect upon the position of the N–H stretching frequencies, in contrast to O–H · · · N intramolecular hydrogen-bonding where the O–H frequency is considerably lowered. The effect may be apparent in 4-methylaminopyrimidine (IV) which gives rise [15] to two N–H stretching vibration absorptions in dilute solution at 3443 and 3466 cm.$^{-1}$, the frequencies falling to 2555 and 2570 cm.$^{-1}$ on deuteration. The absorptions may be due to the " free " form (IVa) and the hydrogen-bonded form (IVb) respectively, the latter giving the higher frequency as the N–H · · · N angle is less than 90° and so causes a larger restoring force for the N–H stretching vibration. The two bands are of comparable intensity, suggesting that the two forms (IVa and b) are equally stable, the increase in stability due to hydrogen-bonding being offset by steric compression between the methyl and *ortho*-CH group in (IVb).

II. *Intensities.*—The integrated intensity (A) of an infrared absorption band is related to the change of the vector dipole moment with the normal co-ordinate of the vibration (dM/dQ) by the expression:

$$A = (N\pi/3c)(dM/dQ)^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

The stretching vibrations of the primary amino-group involve the motions of both of the N–H bonds in the group, and the intensities of the corresponding absorption bands afford a knowledge of the electrical properties of the N–H bonds in a given amine if it is assumed that only the change of the N–H bond moment with bond length (dM/dr) contributes to the transition moment, and that the contributions from the two N–H bonds are equal and additive. With these assumptions the dipole moment gradients of the

[14] Cochran, *Acta Cryst.*, 1948, **1**, 4.
[15] Brown, Hoerger, and Mason, *J.*, 1955, 4035.

normal co-ordinates of the symmetric (dM/dQ_s) and the antisymmetric (dM/dQ_a) stretching vibration of the primary amino-group lie along the internal and the external bisector of the H–N–H angle respectively, and they are connected with the N–H bond-moment gradient (dM/dr) by the relations:

$$(dM/dQ_s) = (2/\mu_s)^{1/2} \cos \theta/2 \, (dM/dr) \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

$$(dM/dQ_a) = (2/\mu_a)^{1/2} \sin \theta/2 \, (dM/dr) \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

where μ_s and μ_a are the reduced masses governing the amplitudes of the atomic motions from equations (1) and (2). By equations (7—9) two independent values of (dM/dr) may be obtained, by use of the intensities of the symmetric and the antisymmetric vibration absorption band respectively; and a measure of the H–N–H bond angle may be derived from the ratio of the two intensities through the approximate relationship:

$$A_a/A_s = \tan^2 \theta/2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

The integrated intensity of an infrared absorption band can be found accurately only by graphical summation, but good approximate values can be obtained by fitting the envelope of the band, if it is symmetrically shaped, to a normal-error curve,[16] or to a Lorentz curve.[17] In the present work it was found that the latter curve corresponded more closely to the observed band envelopes, and, accordingly, the intensities were evaluated by means of the relation: [17]

$$A = (\pi/2)E\Delta\nu_{\frac{1}{2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

where E is the maximum extinction coefficient and $\Delta\nu_{\frac{1}{2}}$ the band half-width. Equation (11) is a good approximation [17] if the effective slit-width is less than 0·4 of the band half-width, or if the intensity is measured at about 75% absorption with larger slit-widths. These conditions were adopted in the present study. The intensities obtained by means of equation (11) were not corrected for the effect of the solvent used, since the expressions proposed [18] for the influence of solvents on the intensities of infrared absorption bands do not account for the relative intensities observed with a given amine in chloroform and carbon tetrachloride solutions.

The measured maximum extinction coefficients and band half-widths for the primary amines studied are recorded in Table 2, together with the change of the N–H bond moment with bond length obtained from the intensities of the symmetric $(dM/dr)_s$ and the antisymmetric $(dM/dr)_a$ stretching vibration bands, and the apparent H–N–H bond angle (α) derived from the ratio of the intensities (equations 7—11). The values obtained for the apparent bond angle (α) are too small, that of the amide ion being as low as 55°, and in the " substituted " aromatic amines the expected relative values are not reproduced (compare θ of Table 1 with α of Table 2). Moreover, the two values of the bond dipole gradient (dM/dr) for a given amine do not agree, that derived from the intensity of the symmetric stretching vibration band being invariably larger than that obtained from the antisymmetric band (Table 2).

Thus the assumptions upon which equations (8) and (9) are based are not fully tenable. In particular, the assumption that the transition moment of the symmetric stretching vibration absorption contains only vector components from the N–H bond dipoles (equation 8) requires modification, as it is probable that the atomic dipole of the lone-pair electrons of the amino-group contribute to the transition moment.[19] During the antisymmetric vibration of the amino-group any change in the hybridisation of one N–H bond

[16] Richards and Burton, *Trans. Faraday Soc.*, 1949, **45**, 874.
[17] Ramsey, *J. Amer. Chem. Soc.*, 1952, **74**, 72.
[18] Polo and Kent, *J. Chem. Phys.*, 1955, **23**, 2376; Brown, *Spectrochim. Acta*, 1957, **10**, 149.
[19] Orville-Thomas, Parons, and Ogden, *J.*, 1958, 1047.

is compensated by a converse change in the hybridisation of the other, leaving the *sp*-ratios and the electron-distributions in the other orbitals of the molecule unaltered. Thus equation (9) is a good approximation. During the symmetric vibration, however, both of the N–H bonds undergo the same change of hybridisation, and a compensating change must occur in the other orbitals of the nitrogen atom, notably, in the lone-pair orbital. Tables of overlap integrals indicate [13] that the " *s* " character of a nitrogen hybrid orbital giving the maximum overlap with a hydrogen 1*s*-orbital falls as the N–H bond length increases. As the N–H bonds lengthen during the symmetric stretching vibration of the amino-group, the " *s* " character of the bonds falls whilst that of the lone-pair orbital increases, and the atomic dipole of the lone-pair electrons, which increases with the " *s* " character of the orbital,[20] makes a significant contribution to the transition moment of the vibration. The contribution is particularly important in the amide ion, which has two pairs of unshared electrons, for the symmetric band is some four times as intense as the antisymmetric band in this case (Table 2), whilst the intensities would be comparable if equation (8) were valid.

In the series of " substituted " aromatic amines the lone-pair electrons of the amino-group are extensively delocalised over the aromatic nucleus in the vibrational ground state. As the " *s* " character of the lone-pair orbital increases during the symmetric vibration, the lone-pair electrons become more localised on the amino-nitrogen atom, since the *s*-orbital, with even symmetry, cannot combine with the π-orbitals of the nucleus, which have odd symmetry with respect to the plane of the molecule. Accordingly, the π-electron component of the permanent dipole of the aromatic amines varies in phase with the symmetric vibration, and so contributes to the transition moment of that vibration, the contribution becoming larger the greater the conjugation between the amino-group and the aromatic nucleus. There are indications that the intensity of the symmetric band becomes progressively larger than required by equation (8) with increasing conjugation in the aromatic series. The apparent bond angle (α), which is an expression of the intensity ratio (A_s/A_a) by equation (10), progressively falls, relative to the bond angle (θ) derived from the frequencies, as the conjugation between the amino-group and the aromatic nucleus increases (Tables 1 and 2). Moreover, the fall is larger in the *para*-" substituted " amines than in their *ortho*-isomers (compare 4 and 8, 5 and 9, 10 and 12, 17 and 18, Tables 1 and 2), the *para*-compounds having larger permanent dipole moments than their *ortho*-isomers (2- and 4-aminopyridine have moments of 2·17 and 4·79 D respectively [21]).

Whilst the intensities of the symmetric stretching vibration bands of the primary amines do not depend upon the electrical properties of the N–H bonds alone, it is probable that the intensities of the antisymmetric bands afford good approximate values of the N–H bond dipole gradient (dM/dr) by equation (9). The values of $(dM/dr)_a$ obtained (Table 2) are ambiguous in sign, and it is found (Fig. 1*B*) that they correlate linearly with the " *s* " character of the N–H bonds if the value for the amide ion has a sign opposite to those of the aliphatic and aromatic amines. On electronegativity grounds it is probable that the N–H bond in the aliphatic and the aromatic amines has the polarity $\bar{N}\text{–}\overset{+}{H}$, so that the polarity in the amide ion is $\overset{+}{N}\text{–}\bar{H}$, the correlation of (Fig. 1*B*) suggesting that the electronegativity of the nitrogen atom increases with the " *s* " character of the N–H bonds.

In the aromatic series the N–H bond dipole gradient $(dM/dr)_a$ increases as the π-electron charge density on the amino-nitrogen atom (q_N) falls (Fig. 2*B*). In general, a decrease in the charge density (q_N) is accompanied by an increase in the " *s* " character of the N–H bonds, but in aniline and 5-aminopyridine the N–H bonds have the same " *s* " character though the bond dipole gradient of the latter compound is larger than that of former (Table 2, Fig. 2*B*), suggesting that the electronegativity of the amino-nitrogen atom is increased by a reduced charge density independently of any changes in hybridisation.

[20] Coulson, *Trans. Faraday Soc.*, 1942, **38**, 433.
[21] Goethals, *Rec. Trav. chim.*, 1935, **54**, 299.

Experimental

Infrared Spectra.—These were measured with a Perkin–Elmer model 12 C spectrometer, with a lithium fluoride prism and a quartz filter. The effective slit width was about 6 cm.$^{-1}$. The aromatic amines were examined at two or more concentrations in the range M/100 to M/1000, in cells of 1 cm. length with chloroform and also 2 and 5 cm. length with carbon tetrachloride as solvent. *cyclo*Hexylamine was examined at M/50-concentration in a 5 cm. path-length of carbon tetrachloride. The intensities recorded in Table 2 refer to solutions giving about 75% absorption with the longest path-lengths employed. These intensities were reproducible within 5%, though they are up to 5% larger than the intensities given by stronger solutions with shorter path-lengths.

Materials.—5-Aminopyrimidine was kindly supplied by Dr. N. Whittaker,[22] 3-amino-6-methyl- and 4-amino-pyridazine by Dr. J. Druey, and 2-aminopyrazine and 2- and 4-amino-pyrimidine by Dr. D. J. Brown. 3-Amino- and 3-amino-5 : 6-dimethyl-1 : 2 : 4-triazine were prepared according to Erickson's directions.[23] The remaining compounds were commercial specimens.

The author thanks Dr. D. H. Whiffen for valuable discussion and advice, and the Australian National University for a Research Fellowship.

Australian National University.
The University, Exeter. [*Received, May 20th*, 1958.]

[22] Whittaker, *J.*, 1951, 1565.
[23] Erickson, *J. Amer. Chem. Soc.*, 1952, **74**, 4706.

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724. *The Constitution of Jute Hemicellulose I.*

By G. O. Aspinall and P. C. Das Gupta.

Partial acid hydrolysis of jute hemicellulose I yields the aldobiouronic acid (2-D-xylose 4-*O*-methyl-α-D-glucopyranosid)uronic acid. Hydrolysis of the methylated polysaccharide affords 2 : 3 : 4-tri-*O*-methyl-D-xylose, 2 : 3-di-*O*-methyl-D-xylose, 3-*O*-methyl-D-xylose, and (3-*O*-methyl-2-D-xylose 2 : 3 : 4-tri-*O*-methyl-α-D-glucopyranosid)uronic acid in the approximate molar ratio 3 : 79 : 4 : 14. The methylated polysaccharide has a molecular weight of 21,000 ± 500 (degree of polymerisation, 123 ± 3). It is concluded that the polysaccharide is composed of chains of *ca.* 108 1 : 4-linked β-D-xylopyranose residues with approximately every seventh residue carrying a terminal 4-*O*-methyl-α-D-glucopyranosiduronic acid residue linked through position 2. A small degree of branching in the backbone of D-xylose residues is indicated.

The various xylans from land plants contain backbones of 1 : 4-linked β-D-xylopyranose residues but differ amongst themselves in molecular size, and in the nature, number, and mode of attachment of other sugar residues linked as side-chains.[1] The xylans from cereals [1] are generally characterised by the presence of L-arabofuranose residues linked to position 3 of xylose, although in several cases uronic acid residues are also present. The xylans from both hard and soft woods [2] all contain 4-*O*-methyl-D-glucuronic acid residues attached as side-chains by 1 : 2-linkages, but some also contain a small proportion of L-arabofuranose residues. The hemicelluloses of the bast fibres have been less extensively studied and this paper describes the structure of a xylan from jute. Some preliminary investigations on this material have been reported.[3,4]

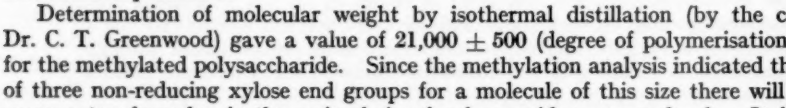
Partial acid hydrolysis of jute hemicellulose I yields xylose and an acidic fraction. On

[1] Hirst, *J.*, 1955, 2974.
[2] Aspinall and McKay, *J.*, 1958, 1059, and references there cited.
[3] Sarkar, Mazumder, and Pal, *Textile Res. J.*, 1952, **22**, 529.
[4] Das Gupta and Sarkar, *ibid.*, 1954, **24**, 705.

the basis of its reaction with periodate the structure (3-D-xylose 3-*O*-methyl-D-glucopyranosid)uronic acid was proposed for the acidic material.[4] Chromatography of this material, however, showed a main component together with three minor components, and a pure sample of the aldobiouronic acid was isolated after separation of the mixture on cellulose.[5] The acidic disaccharide contained residues of 4-*O*-methyl-D-glucuronic acid and D-xylose since conversion into the methyl ester methyl glycoside followed by reduction with lithium aluminium hydride and hydrolysis afforded 4-*O*-methyl-D-glucose and D-xylose. The aldobiouronic acid was established to be (2-D-xylose 4-*O*-methyl-α-D-glucopyranosid)uronic acid since reduction of the methylated derivative with lithium aluminium hydride followed by re-methylation and hydrolysis gave 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose and 3 : 4-di-*O*-methyl-D-xylose. The large positive optical rotations of the aldobiouronic acid and its methylated derivative indicate the presence of an α-glycosidic linkage. The minor acidic components were not examined in detail but it is probable that 4-*O*-methylglucuronic acid and an aldotriouronic acid were present. In addition, reduction and hydrolysis of one fraction afforded galactose and rhamnose, the former probably arising from galacturonic acid. It is likely that these sugars are formed from a small amount of a polysaccharide contaminant since subsequent methylations gave no evidence that they were constituents of the xylan.

Jute hemicellulose was converted into its fully methylated derivative, two main fractions of which were isolated. These fractions had similar physical properties and hydrolysis gave the same sugars but in slightly different proportions. One fraction was examined in greater detail; hydrolysis gave 2 : 3 : 4-tri-*O*-methyl-, 2 : 3-di-*O*-methyl-, and 3-*O*-methyl-D-xylose, and a partially methylated aldobiouronic acid in the approximate molar ratio of 3 : 79 : 4 : 14. The following experiments showed the acidic disaccharide to be (3-*O*-methyl-2-D-xylose 2 : 3 : 4-tri-*O*-methyl-α-D-glucopyranosid)uronic acid. The methylated aldobiouronic acid was converted into the methyl ester methyl glycoside which was reduced with lithium aluminium hydride. Hydrolysis of a portion of the partially methylated disaccharide gave 2 : 3 : 4-tri-*O*-methylglucose and 3-*O*-methylxylose, identified by chromatography and ionophoresis. The remaining material was re-methylated; hydrolysis of the fully methylated disaccharide furnished 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose and 3 : 4-di-*O*-methyl-D-xylose. These results show that the polysaccharide contains chains of 1 : 4-linked β-D-xylopyranose residues with approximately every seventh xylose residue carrying a terminal 4-*O*-methyl-D-glucuronic acid residue attached as a side-chain to position 2.

Determination of molecular weight by isothermal distillation (by the courtesy of Dr. C. T. Greenwood) gave a value of 21,000 ± 500 (degree of polymerisation, 123 ± 3) for the methylated polysaccharide. Since the methylation analysis indicated the presence of three non-reducing xylose end groups for a molecule of this size there will be on the average two branches in the main chain of xylose residues per molecule. It follows also that the branch points must involve 1 : 2-linkages, but at present there is no indication of the length of the side-chains. The accompanying partial structure for the xylan indicates the main features of the molecule.



(D-Xyl*p* = D-xylopyranose, D-G*p*A = 4-*O*-methyl-D-glucuronic acid.)

Probably, in the case of jute hemicellulose, as with other xylans, a range is present of closely-related molecular species of the same general type, which differ in their more detailed structures. This is suggested by the isolation of two fractions of methylated jute

[5] Hough, Jones, and Wadman, *J.*, 1949, 2511; Whistler, Conrad, and Hough, *J. Amer. Chem. Soc.*, 1954, **76**, 1663.

hemicellulose, hydrolysis of which gave slightly different porportions of tri-, di-, and mono-*O*-methyl sugars, and by the fact that the detailed methylation analysis indicated the presence of one uronic acid residue per seven xylose residues, whereas the uronic acid content of the original polysaccharide [3] showed one acid residue per six xylose residues.

This jute xylan then resembles most closely the wood xylans in carrying 4-*O*-methyl-D-glucuronic acid residues as single-unit side-chains attached to position 2 of xylose residues in the main chain. It differs, however, from the wood xylans in that there is clear evidence of branching in the backbone of xylose residues.

[Added, *August 22nd*, 1958.—Since the submission of this paper Srivastava and Adams (*Chem. and Ind.*, 1958, 920) reported conclusions, similar to those described here, regarding the structure of the aldobiouronic acid from jute hemicellulose. From the partial acid hydrolysis of jute fibres they isolated and characterised the same aldobiouronic acid (2-D-xylose 4-*O*-methyl-α-D-glucosid)uronic acid, and identified 4-*O*-methyl-D-glucuronic acid and the acidic trisaccharide, D-Xyl 4 ⟶ 1 β-D-Xyl*p* 2 ⟶ 1 α-D-G*p*A].

Experimental

Jute hemicellulose I was prepared as described previously.[3,4] Paper partition chromatography was carried out on Whatman No. 1 filter paper with the following solvent systems (v/v): (A) butanol–ethanol–water (4 : 1 : 5; upper layer); (B) ethyl acetate–acetic acid–formic acid–water (18 : 3 : 1 : 4); (C) ethyl acetate–acetic acid–water (9 : 2 : 2); (D) butan-2-one, two-thirds saturated with water; (E) light petroleum (b. p. 100—120°)–butanol (7 : 3), saturated with water; (F) benzene–ethanol–water (169 : 47 : 15; upper layer). Paper ionophoresis was in borate buffer at pH 10.

Partial Acid Hydrolysis of Jute Hemicellulose I and Separation of Acidic Oligosaccharides.—Hemicellulose (40 g.) was heated with N-sulphuric acid (2 l.) at 100° for 7 hr. The cooled solution was neutralised with barium hydroxide and barium carbonate, the filtrate was concentrated to small volume, and the solution was poured into ethanol. The precipitated barium salts were extracted with boiling ethanol to remove adhering xylose, and redissolved in water, and the solution was treated with Amberlite resin IR-120(H) to remove barium ions, and concentrated to a syrup. Chromatography in solvent B showed a main component with R_{xylose} 0·85 and others with R_{xylose} 1·14, 0·58, 0·41, and 0·22, the first of these moving at the same rate as 4-*O*-methyl-D-glucuronic acid.

The acidic syrup (3·2 g.) was dissolved in a little water, absorbed on cellulose powder, and freeze-dried, and the mixture was placed on a cellulose column (48 × 4·5 cm.).[5] After elution with solvent C three fractions were isolated and examined further. The main component, fraction 1 (1·2 g.), had R_{xylose} 0·85, $[\alpha]_D^{19}$ +84·7° (*c* 1·5 in H_2O) (Found: OMe, 8·5%; equiv., 368. Calc. for $C_{12}H_{22}O_{11}$: OMe, 9·1%; equiv., 342). Fraction 2 (140 mg.) had R_{xylose} 0·58, $[\alpha]_D^{19}$ +45° (*c* 1·0 in H_2O), and gave xylose and rhamnose as neutral components on hydrolysis; conversion into the methyl ester methyl glycoside, followed by reduction with lithium aluminium hydride and hydrolysis, gave xylose, rhamnose, galactose, 4-*O*-methylglucose, and a trace of glucose. Fraction 3 (260 mg.) had R_{xylose} 0·41, $[\alpha]_D^{19}$ +46° (*c* 2·0 in H_2O), and gave xylose as the only neutral product of hydrolysis; reduction of the methyl ester methyl glycoside and hydrolysis gave xylose, 4-*O*-methylglucose, and a trace of glucose.

Characterisation of Fraction 1 *as* (2-D-*Xylose* 4-O-*Methyl*-α-D-*glucopyranosid*)*uronic Acid.*—The aldobiouronic acid (0·4 g.) was refluxed with methanolic 2% hydrogen chloride, and the resulting methyl ester methyl glycoside was reduced with lithium aluminium hydride in tetrahydrofuran.[6] The product was hydrolysed with N-sulphuric acid at 100° for 7 hr., and after neutralisation with barium carbonate the hydrolysate was separated on filter sheets, solvent A being used, giving fractions *a* and *b*. Chromatography of the sugar and the products of periodate oxidation [7] indicated that fraction *a* was 4-*O*-methylglucose [4-*O*-methyl-D-glucose phenylosazone, identified by m. p. 158—159° and *X*-ray powder photograph (Found: OMe, 8·5; N, 15·4. Calc. for $C_{19}H_{26}O_4N_4$: OMe, 8·3; N, 15·0%)]. Fraction *b* had m. p. and mixed m. p. (with D-xylose) 143°, $[\alpha]_D^{19}$ +18° (*c* 1·0 in H_2O), and was further characterised by conversion into the di-*O*-benzylidene dimethyl acetal, m. p. 211°.

[6] Lythgoe and Trippett, *J.*, 1950, 1983.
[7] Lemieux and Bauer, *Canad. J. Chem.*, 1953, **31**, 814.

Treatment of the aldobiouronic acid (0·7 g.), first with methyl sulphate and sodium hydroxide, and then with methyl iodide and silver oxide gave the methylated derivative (627 mg.), $[\alpha]_D^{18}$ +89° (*c* 1·5 in $CHCl_3$) (Found: OMe, 49·8. Calc. for $C_{18}H_{32}O_{11}$: OMe, 51·2%). Reduction of the methylated aldobiouronic acid with lithium aluminium hydride [6] in ether, followed by methylation with methyl iodide and silver oxide, furnished the fully methylated disaccharide (450 mg.), $[\alpha]_D^{19}$ +93·2° (*c* 1·4 in $CHCl_3$) (Found: OMe, 52·2. Calc. for $C_{18}H_{34}O_{10}$: OMe, 52·9%). Hydrolysis of this (400 mg.) with N-sulphuric acid at 100° for 6 hr. afforded syrupy sugars (300 mg.) which were separated on cellulose (60 × 1·7 cm.) by solvent E into two fractions. Fraction (i) (105 mg.) was 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose, m. p. and mixed m. p. 78—84°, $[\alpha]_D^{18}$ +84° (equil.) (*c* 1·0 in H_2O) (Found: OMe, 52·0. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%). The aniline derivative (from light petroleum) had m. p. and mixed m. p. 126—128°, $[\alpha]_D^{17}$ +206° (*c* 0·5 in $COMe_2$). Chromatography and ionophoresis of fraction (ii) (75 mg.) showed only 3 : 4-di-*O*-methylxylose, and the sugar was characterised by conversion into 3 : 4-di-*O*-methyl-D-xylonolactone, m. p. 66—67°, $[\alpha]_D^{17}$ −20·5° (equil.) (*c* 1·0 in H_2O) (Found: OMe, 34·9. Calc. for $C_7H_{12}O_5$: OMe, 35·2%). The derived aldonamide, after treatment with sodium hypochlorite and addition of semicarbazide, afforded hydrazodicarbonamide, m. p. 256°.

Methylation of Jute Hemicellulose.—The polysaccharide (25 g.) was methylated by successive additions of methyl sulphate and sodium hydroxide, and then with methyl iodide and silver oxide to give methylated jute hemicellulose (27 g.), $[\alpha]_D^{22}$ −32·6° (*c* 0·8 in $CHCl_3$) (Found: OMe, 38·6%). This (20 g.) was fractionated by dissolution in boiling chloroform–light petroleum (b. p. 40—60°), and two main fractions were obtained: (1) {7·5 g., soluble in chloroform–light petroleum (3 : 7), $[\alpha]_D^{25}$ −33·2° (*c* 1·0 in $CHCl_3$); OMe, 38·9%} and (2) {11·8 g., soluble in chloroform–light petroleum (4 : 6), $[\alpha]_D^{25}$ −36·1° (*c* 1·0 in $CHCl_3$); OMe, 38·9%}. Hydrolysis of fraction (1) [*M* (isothermal distillation in benzene), 20,700 ± 500 (degree of polymerisation, 121 ± 3)], and quantitative chromatography [8] of the resulting neutral methylated sugars showed tri-, di-, and mono-*O*-methylxylose in the molar percentages 2·5, 94·2, and 3·3. Hydrolysis of fraction (2) [*M*, 21,000 ± 500 (degree of polymerisation, 123 ± 3)] gave tri-, di-, and mono-*O*-methylxylose in the molar percentages 3·3, 92·1, and 4·6. Fraction (2) was used in subsequent experiments.

Hydrolysis of Methylated Hemicellulose and Separation of Methylated Sugars.—The methylated polysaccharide (6 g.) was hydrolysed successively with boiling methanolic 1% hydrogen chloride (500 ml.) for 9 hr. and with 0·5N-hydrochloric acid (360 ml.) at 100° for 7 hr. Evaporation after neutralisation with silver carbonate yielded a syrup (7 g.), which was treated (in aqueous solution) with barium carbonate. The mixture of methylated sugars was fractionated on cellulose (60 × 3·5 cm.) by solvent D into three fractions, and elution with water gave a fourth fraction, containing barium salts, which was treated with Amberlite resin IR-120(H) to remove barium ions and concentrated to a syrup.

Fraction 1. Chromatography of the syrup (112 mg.) showed 2 : 3 : 4-tri-*O*-methylxylose, but hydrolysis of a portion gave some 2 : 3-di-*O*-methylxylose indicating the presence of unhydrolysed methyl glycoside. After hydrolysis of the syrup with N-hydrochloric acid at 100° for 4 hr., the hydrolysate was separated on filter sheets with solvent D, and 2 : 3 : 4-tri-*O*-methyl-D-xylose (80 mg.) was isolated, m. p. and mixed m. p. 86—87°, $[\alpha]_D^{20}$ +19·9° (equil.) (*c* 0·5 in H_2O) (Found: OMe, 48·0. Calc. for $C_8H_{16}O_5$: OMe, 48·4%).

Fraction 2. The syrup (2·276 g.) crystallised when seeded with 2 : 3-di-*O*-methyl-β-D-xylose and had m. p. and mixed m. p. 78°, $[\alpha]_D^{21}$ −27·9° (2 min.) ⟶ +24° (77 min., const.) (*c* 2·0 in H_2O) (Found: OMe, 34·3. Calc. for $C_7H_{14}O_5$: OMe, 34·8%). The identity was confirmed by conversion of the sugar into 2 : 3-di-*O*-methyl-*N*-phenyl-D-xylosylamine, m. p. and mixed m. p. 123°, $[\alpha]_D^{20}$ +183° (*c* 0·7 in ethyl acetate) (Found: OMe, 24·2; N, 5·6. Calc. for $C_{13}H_{19}O_4N$: OMe, 24·5; N, 5·5%), and 2 : 3-di-*O*-methyl-D-xylonamide, m. p. 132°, $[\alpha]_D^{20}$ +50° (*c* 1·0 in H_2O) (Found: OMe, 31·9; N, 7·4. Calc. for $C_7H_{15}O_5N$: OMe, 32·1; N, 7·25%).

Fraction 3. Chromatography and ionophoresis of the syrup (111 mg.), $[\alpha]_D^{17}$ +15·6° (*c* 1·0 in H_2O), showed 3-*O*-methylxylose and a trace of the 2-methyl ether.

Fraction 4. Chromatography of the syrup (855 mg.) in solvent B showed a main component and small amounts of 2 : 3 : 4-tri-*O*-methylglucuronic acid. The syrup (0·5 g.) was converted into the methyl ester methyl glycoside by refluxing with methanolic 1% hydrogen chloride (100 ml.) for 7 hr. Lithium aluminium hydride in methylal was added slowly to a boiling solution of the ester glycoside in methylal and the mixture was refluxed for 2 hr. Excess

[6] Hirst, Hough, and Jones, *J.*, 1949, 928; Chanda, Hirst, Jones, and Percival, *J.*, 1950, 1289.

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of hydride was destroyed by water, the solution was filtered, methylal was removed under reduced pressure, and the aqueous solution was de-ionised with Amberlite resins IR-120(H) and IR-4B(OH), and concentrated to a syrup (415 mg.). A portion (100 mg.) of the syrup was hydrolysed with N-sulphuric acid at 100° for 6 hr., and chromatography and ionophoresis of the hydrolysate showed 2 : 3 : 4-tri-*O*-methylglucose, 3-*O*-methylxylose, and traces of 2 : 3-di-*O*-methylxylose. Another portion of the syrup was methylated with methyl iodide and silver oxide; hydrolysis of the fully methylated disaccharide with N-sulphuric acid at 100° for 6 hr. gave a mixture which was separated on cellulose (60 × 1·7 cm.) with solvent E into two main fractions *a* and *b*. The sugar (90 mg.) was identified as 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose, m. p. and mixed m. p. 78—84°, $[\alpha]_D^{17}$ +96° ⟶ +83·8° (*c* 1·0 in H_2O) {aniline derivative, m. p. 126—128°, $[\alpha]_D^{17}$ +206° (*c* 0·5 in $COMe_2$)}. Fraction *b* (65 mg.) was shown by chromatography and ionophoresis to be 3 : 4-di-*O*-methylxylose and was identified by conversion into 3 : 4-di-*O*-methyl-D-xylonolactone, m. p. 66—67°, $[\alpha]_D^{17}$ −54° ⟶ −20·5° (66 hr., const.) (*c* 0·8 in H_2O).

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TECHNOLOGICAL RESEARCH LABORATORIES, INDIAN CENTRAL JUTE COMMITTEE, CALCUTTA.
DEPARTMENT OF CHEMISTRY, UNIVERSITY OF EDINBURGH. [*Received, May 12th,* 1958.]

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725. *The Reaction of Organolithium Compounds with Some Halogeno-acetals.*

By GURNOS JONES and H. D. LAW.

Reaction of some organolithium compounds with 3-halogenopropionaldehyde diethyl acetals gives good yields of the acetals $R{\cdot}CH_2{\cdot}CH_2{\cdot}CH(OEt)_2$. The reaction with halogenacetaldehyde diethyl acetals is less uniform, but in one case the acetal $R{\cdot}CH_2{\cdot}CH(OEt)_2$ was obtained in fair yield.

REACTION of bromoacetal with 2-pyridylmethyl-lithium has been shown [1] to give 3-2′-pyridylpropionaldehyde diethyl acetal in 28% yield. As we required 4-2′-pyridylbutyraldehyde for another investigation, we examined the reaction of 2-pyridylmethyl-lithium with 3-chloropropionaldehyde diethyl acetal.

Osuch and Levine [2] have shown that the reaction between 2-pyridylmethyl-lithium and alkyl bromides proceeds in best yield if a 2 : 1 molar ratio of lithium compound to halide is used, and we used this ratio in most of our experiments. The yield of 4-2′-pyridylbutyraldehyde diethyl acetal obtained was 60%, and we were encouraged to test the generality of the reaction. Using 3-bromopropionaldehyde diethyl acetal instead of the chloro-compound gave a lower yield of the acetal (37%), and the chloro-compound was used in subsequent experiments.

Osuch and Levine suggested [2] that 2 mols. of lithium compound are needed because an intermediate complex is formed in which the halide is bonded to the pyridine-nitrogen atom. Since such a complex is not possible with phenyl-lithium we used in our initial reaction between phenyl-lithium and chloropropionaldehyde diethyl acetal a 1 : 1 molar ratio. The yield was disappointingly low (21%) but was increased to 57% by the use of a 2 : 1 molar ratio, and this was used in most of the subsequent experiments. Thus, *n*-butyl-lithium gave with the chloroacetal a 63% yield of *n*-heptaldehyde diethyl acetal.

[1] Wibaut and Beets, *Rec. Trav. chim.*, 1940, **59**, 653; 1941, **60**, 905; Spielman, Swadesh, and Mortenson, *J. Org. Chem.*, 1941, **6**, 1780.
[2] Osuch and Levine, *J. Amer. Chem. Soc.*, 1956, **78**, 1723.

These results are assembled in Table 1. All acetals were identified by their infrared absorption, and by hydrolysis and preparation of derivatives of the aldehyde.

Since good yields were obtained with the halogenopropionaldehyde acetals we attempted to extend the scope of the reaction between 2-pyridylmethyl-lithium and bromoacetaldehyde diethyl acetal previously mentioned. By using a molar ratio of 2 : 1 we obtained 3-2′-pyridylpropionaldehyde diethyl acetal in 38% yield from the bromoacetal, but the chloroacetal under similar conditions gave a higher yield (49%). However, attempts to perform similar syntheses with other, more reactive lithium compounds were

$$RLi + X{\cdot}CH_2{\cdot}CH(OEt)_2 \longrightarrow R{\cdot}X + Li{\cdot}CH_2{\cdot}CH(OEt)_2 \quad (I) \qquad (1a)$$

$$Li{-}CH_2{-}CH(OEt){-}OEt \longrightarrow CH_2{:}CH{\cdot}OEt + LiOEt \qquad (1b)$$

unsatisfactory. Thus phenyl-lithium and a bromoacetal reacted violently, but the sole product isolated was bromobenzene (76%, based on bromoacetal). If the reaction is a halogen–metal interchange (1*a*) it is to be expected that the intermediate lithium compound (I) would lose lithium ethoxide as shown in (1*b*) to give ethyl vinyl ether. No attempt was made to isolate ethyl vinyl ether from the large volume of diethyl ether used as solvent, but the absence of acetaldehyde diethyl acetal [the product expected when the lithium compound (I) is treated with water] appears to indicate that the lithium compound (I) if formed is unstable.

The reactions of phenyl-lithium or of butyl-lithium with chloroacetal [25] were less informative, much chloroacetal being recovered in both cases, together with uncharacterized low-boiling materials. In neither case was even a trace of the expected acetal found, and so no further experimental modifications were attempted. Summers and Larson have recorded [3] a reaction between phenyl-lithium and 1-bromo-2-ethoxyethane in which ethyl phenethyl ether was obtained: using their conditions (inverse addition; reaction in the cold) we obtained from phenyl-lithium and the bromoacetal some bromobenzene and some unchanged bromoacetal. Attempted reaction of phenylmagnesium bromide with 3-chloropropionaldehyde diethyl acetal in the presence of a trace of ferric chloride [4] gave only 8% of 3-phenylpropionaldehyde diethyl acetal, 90% of the chloroacetal being recovered after 4 hours' boiling of the ethereal solution. After a similar period of reaction in boiling benzene the yield of acetal was the same, but the recovery of chloroacetal was smaller.

Experimental

M. p.s were determined on a Kofler block. 3-Bromopropionaldehyde diethyl acetal [5] and 3-chloropropionaldehyde diethyl acetal [6] were synthesized from acraldehyde. All acetals were dried (K_2CO_3) and distilled immediately before use.

4-2′-Pyridylbutyraldehyde Diethyl Acetal.—A filtered solution of 2-pyridylmethyl-lithium, prepared [7] from bromobenzene (0·2 mole), lithium (0·2 mole), and 2-picoline (0·2 mole) in ether (180 ml.) was stirred under dry nitrogen while 3-chloropropionaldehyde diethyl acetal (0·1 mole) was added. The mixture boiled for 15 min. after the addition without external heating. The mixture was stirred at the b. p. for 4 hr. during which much white solid separated, and was then set aside overnight at room temperature. The cooled mixture was hydrolysed by addition of dilute ammonia and ammonium chloride, the ethereal layer was separated, and the aqueous layer was extracted twice with small portions of ether. The combined ethereal extracts were dried (K_2CO_3) and distilled. The acetal boiled at 143—145°/12 mm. (13·3 g., 60%), and contained traces of diphenyl (<3%). A sample was dissolved in cold dilute hydrochloric acid, and after a few min. diluted and treated with aqueous sodium picrate. The *aldehyde picrate*

[3] Summers and Larson, *J. Amer. Chem. Soc.*, 1952, **74**, 4498.
[4] Vavon and Mottez, *Compt. rend.*, 1944, **218**, 557.
[5] Nef, *Annalen*, 1904, **335**, 263.
[6] Witzemann, Evans, Hass, and Schroeder, *Org. Synth.*, Coll. Vol. II, p. 137.
[7] Woodward and Kornfeld, *ibid.*, Coll. Vol. III, p. 413.

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crystallized from water as yellow prisms, m. p. 131—132° (Found: C, 47·5; H, 3·7. $C_{15}H_{14}O_8N_4$ requires C, 47·6; H, 3·7%).

The above procedure was used in the experiments recorded in Tables 1 and 2.

TABLE 1. *Reactions of* $X{\cdot}CH_2{\cdot}CH_2{\cdot}CH(OEt)_2$.

Lithium compound	X	Product	Yield (%)	B. p./mm.
2-$C_5H_4N{\cdot}CH_2$–	Cl	2-$C_5H_4N{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH(OEt)_2$	60	143—145°/12
,, ...	Br	2-$C_5H_4N{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH(OEt)_2$	37	143—145°/12
Ph	Cl	$Ph{\cdot}CH_2{\cdot}CH_2{\cdot}CH(OEt)$ [a]	57	106—107°/10
Bu^n	Cl	$CH_3{\cdot}[CH_2]_2{\cdot}CH(OEt)_2$ [b]	63	54—57°/9

[a] Aldehyde *p*-nitrophenylhydrazone, m. p. 122—124°; semicarbazone, m. p. 123—125°. [b] Aldehyde *p*-nitrophenylhydrazone, m. p. 108°; semicarbazone, 74°.

TABLE 2. *Reactions with* $X{\cdot}CH_2{\cdot}CH(OEt)_2$.

Lithium compound	X	Product	Yield (%)	B. p./mm.
2-$C_5H_4N{\cdot}CH_2$–	Cl	2-$C_5H_4N{\cdot}CH_2{\cdot}CH_2{\cdot}CH(OEt)_2$ [a]	49	131°/12 [b]
,, ...	Br	2-$C_5H_4N{\cdot}CH_2{\cdot}CH_2{\cdot}CH(OEt)_2$	38	131°/12
Ph	Cl	— [c]	—	—
Ph	Br	PhBr [d]	76	152—153°/758
Bu^n	Cl	Mixture of low b. p. [e]	—	—

[a] Aldehyde, b. p. 118°/13 mm. (lit.,[3] b. p. 106—108°/9 mm.); aldehyde picrate, m. p. 122·5° (yellow prisms) (Found: C, 46·25; H, 3·1. Calc. for $C_{14}H_{13}O_8N_4$: C, 46·1; H, 3·3%). [b] Lit.,[1] b. p. 128°/8 mm. [c] 90% of chloroacetal recovered. [d] In an experiment using PhLi (0·1 mole) and bromoacetal (0·1 mole) with inverse addition, some unchanged bromoacetal was isolated. [e] 30% of chloroacetal recovered.

Reaction of Phenylmagnesium Bromide with 3-Chloropropionaldehyde Diethyl Acetal.—(*a*) To the filtered Grignard reagent from bromobenzene (0·1 mole) in ether (150 ml.) was added a trace of ferric chloride,[4] and the mixture was boiled under reflux for 4 hr., then left overnight at room temperature. Working up as described above gave 3-phenylpropionaldehyde diethyl acetal (8%) and unchanged chloroacetal (90%). (*b*) In a similar experiment the ether was replaced by benzene (150 ml.) after addition of the chloroacetal, and boiling under reflux was for 4 hr. The yield of phenylpropionaldehyde diethyl acetal was 8%, and 60% of the chloroacetal was recovered.

DEPARTMENT OF CHEMISTRY, UNIVERSITY COLLEGE OF NORTH STAFFORDSHIRE, KEELE, STAFFS.

[*Received, May 28th*, 1958.]

[3] Miller, *J. Amer. Chem. Soc.*, 1953, **75**, 4849.

726. *The Polonium Nitrates.*

By K. W. BAGNALL, D. S. ROBERTSON, and M. A. A. STEWART.

Polonium tetranitrate and two basic nitrates have been prepared and evidence for the existence of a nitrite has been obtained. The cation-exchange behaviour of polonium in nitric acid solution has been investigated.

THE only available data on the polonium–nitric acid system are Orban's solubility determinations[1] and some fragmentary information suggesting the probability of a basic nitrate from this laboratory.[2] Orban, who determined the concentration of polonium in the aqueous phase in contact with oxidised polonium on a platinum foil, found that the solubility of quadrivalent polonium in dilute nitric acid was extremely low, suggesting the formation of a basic salt. The higher solubilities at higher nitric acid concentrations indicate complex-ion formation. Some solubility determinations with carrier-free polonium made here were in fair agreement with Orban's, and it was of interest to attempt the analysis of the solid nitrate.

[1] Orban, American report MLM-973, 1954.
[2] Bagnall and D'Eye, *J.*, 1954, 4295; Bagnall, D'Eye, and Freeman, *J.*, 1955, 2320.

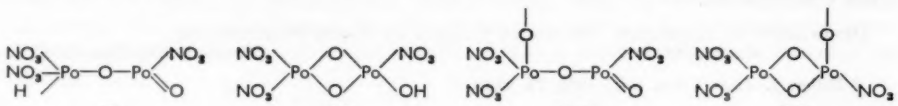
XUM

Preliminary experiments showed that solid polonium hydroxide or tetrachloride reacted immediately with dilute (0·1—2N) nitric acid to give a white, crystalline solid which readily decomposed to polonium dioxide under vacuum or on heating and was readily hydrolysed to the quadrivalent hydroxide. All attempts to analyse it failed and it is probably an unstable addition compound ($PoO_2,xHNO_3$). Both polonium hydroxide and tetrachloride, however, on long standing (12 hr.) in 0·5N-nitric acid, gave a white crystalline product which could be dried under vacuum at room temperature with only slight decomposition. In this compound, *A*, the ratio NO_3^- : Po = 1·5 : 1. The analyses of a similar yellowish-white product, *B*, formed by evaporating the solution obtained from polonium hydroxide and 2N-nitric acid to small volume and finally drying under vacuum, were less consistent, but indicated a ratio NO_3^- : Po = 0·5 : 1 analogous to the only known tellurium nitrate.[3]

The white product obtained by keeping polonium metal in air for 72 hr. or, more rapidly, in a mixture of nitrogen dioxide and oxygen, was found to have the same composition as *A*, the results being very consistent. The fixation of nitrogen by the α-bombardment supplied the nitrogen dioxide in the first method.

Compound *A* is readily decomposed by water, dilute aqueous potassium hydroxide, or dilute hydrochloric acid, giving the quadrivalent hydroxide or chloride. It decomposes to *B* below 100° and *B* decomposes to polonium dioxide at about 130°; attempts to determine the decomposition temperature accurately were frustrated by the slow spontaneous decomposition of the compound under the intense α-bombardment. Both *A* and *B* yield polonium metal by way of the dioxide on long standing in a stream of dry nitrogen or under vacuum. *X*-Ray powder photographs of these compounds have not yet had sufficient definition to provide any information about their structure. Indeed, by the nature of the materials, such evidence may always fall short of that required to justify an unequivocal statement. As further work is likely to be postponed, it may be useful to put forward some tentative conclusions.

Both compounds probably have a dimeric (or polymeric) oxygen-bridge structure, for, as a monomer, *A* could be represented as (I) or (II), in which one would expect a single nitrate ion to be eliminated as nitric acid on heating, rather than a pair of nitrate ions as



nitrogen dioxide and oxygen. A more probable structural unit appears to be (III) or (IV) with the latter, which is symmetrical, as the most likely.

White crystalline compounds were also obtained by the action of aqueous M-potassium nitrate or nitrite on solid polonium tetrachloride. These are presumably a polonium nitrate and a nitrite; they could not be analysed owing to the difficulty of removing the excess of reagent and because both were converted into the quadrivalent hydroxide on standing in contact with an excess of the aqueous reagent for a few hours.

The reactions of polonium dioxide and polonium tetrachloride with liquid dinitrogen tetroxide were then investigated. The white product thus formed was the tetranitrate, $Po(NO_3)_4$, with at least one molecule of dinitrogen tetroxide of crystallisation. The tetranitrate is almost insoluble in liquid dinitrogen tetroxide and is very easily hydrolysed. The N_2O_4 of crystallisation was partially lost when the preparation was freed from excess of dinitrogen tetroxide under vacuum and the remainder very soon on standing at room temperature in dry air. The tetranitrate slowly decomposes in air at room temperature giving the basic salt *A*, the conversion being complete in 1½—2 hr. under vacuum (15 μ).

[3] Norris, according to Mellor, "A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Vol. XI, Longmans, Green & Co., London, 1931, p. 119.

XUM

It is noteworthy that polonium dioxide, after being heated above 250°, scarcely reacts with either gaseous or liquid dinitrogen tetroxide and the metal fails to react at all with either the liquid or its solution in ethyl acetate.

Ion-exchange Data.—The cation-exchange behaviour of polonium in dilute nitric acid showed a trend similar to that observed in the solubility curve.[1] The distribution ratio, K_r, defined as the concentration of polonium/g. of resin divided by the concentration of polonium/ml. of solution, decreases markedly as the acid concentration increases (see Table).

$[HNO_3]$ (N)		0·1	0·2	0·4	0·6	0·8	0·9	1·0	2·0	8·0
Resin	Zeo-Karb 225 40/60 mesh (K_r) ...	366	126	42	28	9·9	7·0	6·5	3·2	~0
	Amberlite IR-120(H) 40/60 mesh (K_r) ...	—	—	16·1	10	—	6	—	5	—

The results were not very reproducible owing to radiation damage to both solvent and resin, and it is not possible to draw any definite conclusions concerning the nature of the ionic species in the solutions.

Experimental

All the experimental work was carried out in glove-boxes.[2]

Preparative.—Specimens made by the action of dilute nitric acid on the solid tetrachloride or hydroxide were allowed to stand in contact with the acid before being dried for analysis; the best results were obtained with amounts of polonium in the range 200—400 μg. of ^{210}Po; analyses of larger specimens were usually very much less consistent, probably owing to radiation damage. The most consistent analytical results were obtained with specimens prepared by the action of oxygen–nitrogen dioxide mixtures on the metal, but the method is very slow if thick layers of metal are used. The optimum is 100—150 μg. of ^{210}Po. The reaction of polonium dioxide or tetrachloride with liquid dinitrogen tetroxide is complete in about 4 hr.

Liquid dinitrogen tetroxide was prepared by heating lead nitrate, drying the evolved gases with phosphoric oxide, and condensing them in a cooling bath.[4]

Analytical.—The main problem in the analysis of sub-milligram amounts of the nitrates lay in the removal of the excess of nitric acid. A preparation carried out with 1 curie (222 μg.) of ^{210}Po would contain 4×10^{-6} g.-ions of nitrate if a tetranitrate were formed and it was therefore necessary to reduce the excess of nitrate-ion content to below 10^{-7} g.-ion, equivalent to 5×10^{-5} ml. of 2N-nitric acid, which was used for some preparations. It was soon found that insufficient of the excess of nitric acid could be eliminated by centrifugation through a number 3 porosity filter pad and that washing with dry acetone was ineffective, while washing with water led to hydrolysis.

The preparations were then dried for 25 min. at 130—150°c, but this yielded only the dioxide; in the course of these analyses it was found that the correction to be applied for the fixation of nitrogen by the α-bombardment of air in alkaline solution was quite small. Vacuum-drying at 50° also led to decomposition. It was finally found that little decomposition occurred if the preparation, together with its excess of nitric acid, was frozen and then dried under vacuum (15 μ) at room temperature for 20 min. Blank runs with nitric acid only showed that this procedure eliminated it all.

The dried polonium nitrate was then decomposed with 0·5N-potassium hydroxide (0·5 ml.); the low hydroxide concentration is necessary to avoid loss of the polonium into the aqueous solution as polonite.[5]

The insoluble polonium hydroxide was then filtered off on a number 3 porosity filter stick and dissolved in 2N-hydrochloric acid for assay by α-counting. The filtrate, containing the nitrate ion for analysis, was transferred to a Conway micro-diffusion cell for final acidimetric assay as ammonia.[6] An "Agla" micro-burette was used for the final titration with 0·02N-hydrochloric acid. All the analytical preparations were carried out in groups of three, together with a fourth "blank" preparation in which all the reactions were carried out without polonium.

[4] Bagnall, Robinson, and Stewart, *J.*, 3426.
[5] Bagnall and Freeman, *J.*, 1957, 2161.
[6] Conway, "Microdiffusion Analysis and Volumetric Error," Crosby Lockwood and Son, Ltd., London, 1947, p. 85.

XUM

Qualitative experiments showed that a part of the nitrate ion was reduced to nitrite by the α-bombardment during the separation for analysis.

Ion Exchange.—A known quantity of the resin (50—100 mg.) was equilibrated with acid of the same concentration as that to be used in the exchange experiment. The excess of acid was then removed and the polonium solution (100—250 mc/5 ml. of acid) was added, and the solution and resin stirred by means of an air-pulsed agitator.[7] Sampling showed that equilibrium was attained in 1½—2 hr. The concentration of polonium in the resin was calculated from the decrease in concentration of polonium in the aqueous phase. It was not possible to determine the distribution ratio of the polonium between the resin and fresh batches of acid owing to the decomposition of the resin by radiation.

UNITED KINGDOM ATOMIC ENERGY AUTHORITY,
A.E.R.E., HARWELL, BERKS.

[*Received, June 18th,* 1958.]

[7] Bagnall and Miles, *J. Sci. Instr.*, 1953, **30**, 172.

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727. *The Vapour Pressures of Nitric Acid Solutions. Part III.*[1] *The Deuterium Oxide–Dinitrogen Pentoxide System.*

By J. G. DAWBER and P. A. H. WYATT.

Vapour pressures and compositions at 0° are reported for the deuterium oxide–dinitrogen pentoxide system in the range 43—90% of N_2O_5. Minima in the total vapour-pressure curve, similar to those in the corresponding water system, are observed at 53·0% and 86·2% of N_2O_5. The vapour pressure of pure DNO_3 (*i.e.*, 84·37% of N_2O_5) is 15·03 mm. Hg at 0°, over 7% higher than that of pure HNO_3, but the heats of vaporization of the two compounds are similar. The extent of self-dissociation of liquid DNO_3 is similar to that of HNO_3.

IN Part I[1] vapour pressures in the dinitrogen pentoxide–water system were reported. We now present data for the corresponding deuterium oxide system for comparison. The substitution of an atom in a molecule by a heavier isotope is in some cases accompanied by an increase,[2,3] and in others by a decrease,[3,4] in the vapour pressure. Our data show that the deuteration of nitric acid falls into the former category since the vapour pressure of the deuterium compound is the greater by more than 7%, although the vapour-pressure minimum at higher dinitrogen pentoxide concentrations[1] still shows clearly. Of more chemical interest is the effect of the heavy isotope on the extent of dissociation of liquid nitric acid. Gillespie and his co-workers[5] have recently shown that dideuterosulphuric acid is appreciably less dissociated than sulphuric acid itself, but our measurements show that this effect is small in the case of nitric acid.

EXPERIMENTAL

The vapour-pressure technique was described in Part I.[1] All solutions were made up by weight and their compositions checked by acidimetry. Dinitrogen pentoxide was distilled from a nitric acid–phosphoric oxide mixture in a stream of ozone[6] and then mixed with a further quantity of phosphoric oxide before resublimation into a cooled, weighed quantity of deuterium oxide (Norsk Hydro 99·8%). After transfer of about 35 g. of this solution to the

[1] Part I, Lloyd and Wyatt, *J.*, 1955, 2248; Part II, *idem*, *J.*, 1957, 4268.
[2] Claussen and Hildebrand, *J. Amer. Chem. Soc.*, 1934, **56**, 1820; Lewis and Schutz, *ibid.*, p. 493; Bates, Haford, and Anderson, *J. Chem. Phys.*, 1935, **3**, 415.
[3] Baertschi, W. Kuhn, and H. Kuhn, *Nature*, 1953, **171**, 1018; *Helv. Chim. Acta*, 1957, **40**, 1084 (cf. Bradley, *Nature*, 1954, **173**, 260).
[4] Lewis and Schutz, *J. Amer. Chem. Soc.*, 1934, **56**, 494, 1002; Widiger and Brown, *ibid.*, 1939, **61**, 2453; Kirshenbaum and Urey, *J. Chem. Phys.*, 1942, **10**, 706; Armstrong, Brickwedde, and Scott, *ibid.*, 1953, **21**, 1297; Giguère, Morisette, Olmos, and Knop, *Canad. J. Chem.*, 1955, **33**, 804.
[5] Flowers, Gillespie, Oubridge, and Solomons, *J.*, 1958, 667.
[6] Dunning and Nutt, *Trans. Faraday Soc.*, 1951, **47**, 15.

cell and measurement of its vapour pressure, additions of deuterium oxide were made and measurements carried out as described for the water–dinitrogen pentoxide system.[1] Vapour samples were collected for analysis at certain points and the liquid composition was corrected accordingly.

Results

Concentration Scales.—Compositions may be referred to as $a\%$ of DNO_3, $b\%$ of N_2O_5, or $c\%$ of "free N_2O_5." The relationships for the deuterium oxide system are $b = 0{\cdot}8437a$, and $c = 6{\cdot}40(b - 84{\cdot}37)$. For simplicity all compositions in Table 1 are quoted as $b\%$ of N_2O_5.

The qualitative features of the vapour-pressure curve are similar to those for ordinary nitric acid (see Part I,[1] Fig. 2). There is a minimum on each side of the composition DNO_3, that on the D_2O side being displaced slightly in the direction to be expected from the greater volatility of DNO_3 and the smaller volatility of D_2O than of the corresponding hydrogen compounds. In the D_2O–DNO_3 region application of the Duhem–Margules equation gave p_{D_2O} values at 93·05, 86·48, 83·61, 80·18, 77·00, 74·79, 71·55, 69·52, 66·10, and 59·45% DNO_3 of 0·01, 0·05, 0·08, 0·15, 0·25, 0·34, 0·49 (fixed), 0·57, 0·75, and 0·96 mm. Hg respectively, whilst the observed values (from the vapour analyses) were 0·04, 0·04, 0·08, 0·12, 0·26, 0·36, 0·49, 0·57, 0·73, and 0·96 mm. Hg. This test was less successful in the N_2O_5–DNO_3 system, where at compositions of 85·10, 85·79, 86·53, 86·92, 87·24, 87·52, 87·75, and 88·02% of N_2O_5 the calculated values of p_{DNO_3} were 14·9, 14·1, 12·7 (fixed), 11·9, 11·3,

Table 1. *Vapour pressures of* N_2O_5 *solutions at* 0°.

(*a*) N_2O_5 concentrations greater than 84·37% (100% DNO_3).

N_2O_5 in liquid (%)	p (mm. Hg)	N_2O_5 in vapour (%)	N_2O_5 in liquid (%)	p (mm. Hg)	N_2O_5 in vapour (%)	N_2O_5 in liquid (%)	p (mm. Hg)	N_2O_5 in vapour (%)
89·68(s)	57·49	—	87·70	22·21	—	86·03	14·18	—
89·38(s)	57·58	—	87·55	20·40	—	85·77	14·31	—
89·13(s)	57·61	—	(87·52)	(19·95)	92·5	(85·79)	(14·27)	85·2
(88·75)	(57·6)	98·7 *	87·49	19·49	—	85·81	14·23	—
88·57	45·26	—	87·31	17·91	—	85·67	14·37	—
(88·52)	(43·13)	97·4(?)	(87·24)	(17·20)	90·5	85·58	14·41	—
88·47	41·01	—	87·17	16·49	—	85·46	14·51	—
88·32	35·93	—	86·94	15·63	—	85·32	14·62	—
88·06	29·39	—	(86·92)	(15·32)	89·0	85·09	14·80	—
(88·02)	(28·39)	96·5	86·89	15·01	—	(85·10)	(14·80)	84·6
87·98	27·39	—	86·54	14·37	—	84·85	14·97	—
87·81	24·34	—	(86·52)	(14·37)	87·1	84·43	15·02	—
(87·75)	(23·28)	94·3	86·28	14·14	—	(84·37)	(15·03)	—

(*b*) N_2O_5 concentrations less than 84·37% (100% DNO_3).

(84·37)	(15·03)	—	77·92	10·94	—	63·49	2·12	—
84·05	14·98	—	77·35	10·49	—	(63·08)	(2·03)	79·0
83·61	14·87	—	76·66	9·98	—	61·45	1·75	—
83·48	14·84	—	76·10	9·49	—	60·38	1·56	73·9
83·17	14·68	—	75·49	9·02	—	58·66	1·45	70·1
82·86	14·59	—	73·30	7·17	—	56·91	1·34	—
82·62	14·44	—	(72·95)	(6·91)	84·2	55·77	1·32	61·5
81·61	13·74	—	70·69	5·19	—	54·64	1·30	58·6
81·36	13·61	—	(70·57)	(5·11)	83·4	52·96	1·26	—
80·32	12·87	—	67·83	3·58	—	50·13	1·32	46·0
80·02	12·58	—	67·62	3·50	83·4	47·44	1·38	35·1
79·20	11·99	—	65·35	2·60	—	43·18	1·60	22·0
(78·50)	(11·40)	84·3	(64·98)	(2·50)	80·9			

Figures in parentheses are interpolated.
* Calculated by using the v. p. of solid N_2O_5 at 0°, viz. 50·0 mm. Hg. (ref. 12).

10·5, 9·8, and 9·1 mm. Hg and the observed 14·7, 13·8, 12·7, 12·2, 12·4 (?), 12·1, 11·4, and 9·3 mm. Hg. The obvious drift is probably due to the difficulty of preventing water

contamination of the vapour samples at the higher N_2O_5 concentrations rather than to any chemical complications in the vapour.[7]

The Self-dissociation of Deuteronitric Acid.—From a graph[8] of $\Delta \log_{10} p_{DNO_3}/\Delta m_2$ against $\bar{m}_2$ (where m_2 represents the molality of D_2O in the solvent DNO_3), it was estimated that $\partial^2 \log_{10} p_{DNO_3}/\partial m^2_2$ is $-(75 \pm 3) \times 10^{-3}$ at $\bar{m}_2 = 0$. Hence,[8] $\alpha_0 = 0{\cdot}024abs/(a + b)$, where α_0 represents the degree of dissociation of pure DNO_3, a and b the numbers of particles formed in solution per molecule of D_2O and N_2O_5 respectively, and s the number of DNO_3 molecules involved in the dissociation equation. For the general dissociation scheme

$$sDNO_3 \rightleftharpoons D_2O,DNO_3 + NO_2^+(DNO_3)_x + NO_3^-(DNO_3)_y$$

in which a D_2O molecule yields one particle and an N_2O_5 molecule 2 particles, *i.e.*, $a = 1$, $b = 2$, we conclude that $\alpha_0/s = 0{\cdot}016$; the value of α_0 depends upon the degree of solvation assumed for the dissociation products. The total molality of dissociation products in the pure acid is not arbitrary in this respect, however, for it is given by $3m_1\alpha_0/s$, *i.e.*, $0{\cdot}048m_1$, or 0·75m. When the data are sufficiently precise, calculation of the extent of dissociation in this way is preferred to the method adopted in Part II,[1] since it does not depend upon measurements for solutions of much greater concentration than the dissociation products in the pure acid.

Since, however, the results[1] for ordinary nitric acid were more scattered than those presented here, the extents of dissociation of the two acids were compared by the method of Part II, *viz.*, plotting the solvent partial pressure against m_2/m_1 and extrapolating the straight line obtained at higher concentrations back to the abscissa at the vapour pressure of the pure solvent. [Applied in this simple form, the latter method tends to give an underestimate since the residual solvent dissociation at higher concentrations is ignored (cf. Gillespie[9]). It is however quite adequate for demonstrating any significant *difference* in the extents of dissociation of two solvents.] By this method both acids yielded the same (low) results for the molality of dissociation products of $0{\cdot}037m_1$, showing that their

TABLE 2. *Vapour pressures of deuteronitric acid–potassium nitrate mixtures at* 0° *and* 20°. (*The deutero-nitric acid contained a slight excess of deuterium oxide.*)

Mole of KNO_3/mole of DNO_3	0·000	0·0211	0·0419	0·0631	0·0905	0·1217
p (mm. Hg) at 0°	14·98	14·60	14·04	13·42	12·51	11·44
p (mm. Hg) at 20°	49·77	48·51	46·57	44·63	42·04	38·99
Mole of KNO_3/mole of DNO_3	0·1579	0·1884	0·2231	0·2889	0·4103	
p (mm. Hg) at 0°	10·29	9·09	7·92	7·72 (s)	7·73 (s)	
p (mm. Hg) at 20°	35·61	31·68	27·94	21·06	15·22 (s)	

(s) indicates that some solid remained undissolved.

extents of dissociation must be very similar. The KNO_3 data lead to the same conclusion, but are not given great weight in view of the slight excess of D_2O (~0·3%) in the initial acid. The vapour pressures of this acid at 0° and 20° (Table 2) yield a heat of vaporization of 9·55 kcal. mole^{-1}, which is close to that for nitric acid itself (*viz.*, 9·44,[10] 9·65,[11] or 9·56[12] kcal. mole^{-1}).

We thank Imperial Chemical Industries Limited for the gift of deuterium oxide and the University of Sheffield for a postgraduate scholarship to J. G. D.

SHEFFIELD UNIVERSITY. [*Received, June 26th,* 1958.]

[7] Wyatt, *Trans. Faraday Soc.*, 1954, **50**, 352.
[8] Wyatt, *ibid.*, 1956, **52**, 806.
[9] Gillespie, *J.*, 1950, 2493; see p. 2499.
[10] Wilson and Miles, *Trans. Faraday Soc.*, 1940, **36**, 356.
[11] Berl and Saenger, *Monatsh.*, 1929, **54**, 1036.
[12] Lloyd, Ph.D. thesis, Sheffield, 1956.

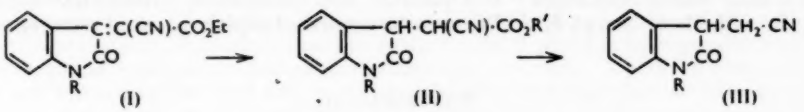
728. *Hydroxytryptamines. Part IV.* Synthesis and Reactions of 2-3′-Oxindolylethylamines.*

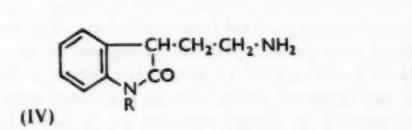
By JOHN HARLEY-MASON and R. F. J. INGLEBY.

2-3′-Oxindolylethylamine is readily obtained in four stages from isatin *via* its condensation product with ethyl cyanoacetate. The 1-methyl derivative is obtained similarly. Reaction with benzaldehyde gave 2′-phenyloxindole-3-*spiro*-3′-pyrrolidines.

3-Oxindolylglyoxylic acid has been obtained by a new route and some earlier reports concerning its rearrangement have been clarified.

A RECENT synthesis by Witkop and his collaborators [1] of 2-3′-oxindolylethylamine (2-hydroxytryptamine) (IV; R = H) in low yield from tryptamine prompts us to record our earlier work [2] on the synthesis of the amine and some derivatives from isatin. Isatin was condensed with ethyl cyanoacetate, piperidine being used as catalyst, to give ethyl α-cyano-3-isatylideneacetate [3] (I; R = H) which was reduced to the oxindolyl ester (II; R = H, R′ = Et). Brief alkaline hydrolysis gave the acid (II; R = R′ = H) which was readily decarboxylated to β-3-oxindolylacetonitrile (III; R = H); this had earlier been obtained by another route.[4] Hydrogenation of the nitrile over Adams's catalyst in acid solution gave the amine (IV; R = H) provided that hydrogenation was





interrupted after 2 mols. of hydrogen had been absorbed. A similar sequence, starting with *N*-methylisatin (of which an improved preparation is described), led to the 1-methylamine (IV; R = Me). The 1-benzyl-nitrile (III; R = benzyl) was obtained similarly but its reduction to the amine was unsatisfactory.

The amines readily underwent an internal Mannich reaction with benzaldehyde giving 2′-phenyloxindole-3-*spiro*-3′-pyrrolidines (V; R = H and R = Me). That the products were not the isomeric Schiff's bases was shown by their stability to acid. Only one product was formed in each case despite the fact that the structure (V) contains two asymmetric centres. Examination of a model showed clearly that in one of the two possible configurations (not illustrated) interference between the two benzene rings is so great that it is most unlikely to be formed, and that our products must have the configuration illustrated, the reaction being stereospecific. A similar ring system occurs in the alkaloid rhyncophylline,[5] and the biogenetic parallel is of interest.

Short boiling of the isatylidene ester (I; R = H) with alkali followed by acidification gave a bright yellow acidic product, corresponding in composition and melting point to

* Part III, *J.*, 1955, 374.

[1] Freter, Weissbach, Redfield, Udenfriend, and Witkop, *J. Amer. Chem. Soc.*, 1958, **80**, 983.
[2] Ingleby, Dissertation, Cambridge, 1956.
[3] Cf. Yokayama, *J. Chem. Soc. Japan*, 1936, **57**, 251.
[4] Cornforth, Cornforth, Dalgliesh, and Neuberger, *Biochem. J.*, 1951, **48**, 591.
[5] Seaton and Marion, *Canad. J. Chem.*, 1957, **35**, 1102.

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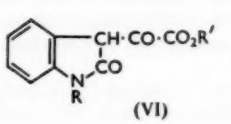
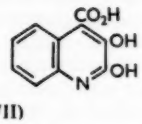
Granacher and Mahal's [6] 3-oxindolylglyoxylic acid (VI; R = R′ = H); hydrogen cyanide was also obtained, so that the reaction clearly involved displacement of the cyano-group by hydroxyl in addition to hydrolysis of the ester. However, later [7] Granacher and Kouniniotis assigned a revised structure, 2 : 3-dihydroxyquinoline-4-carboxylic acid (VII), to their product, and this revision has been supported.[8]



(VI)



(VII)

The ethyl ester (VI; R = H, R′ = Et) was prepared later by Horner [9] from oxindole and ethyl oxalate and was hydrolysed to the acid (assigned the unrearranged structure). We have now found that the absorption spectra of the ester and the free acid are very similar and further, that the acid is readily re-esterified to the original ester, so that rearrangement does not take place during the hydrolysis. Furthermore, we have found that 3-oxindolylglyoxylic acid is *not* rearranged even on prolonged boiling with acid or alkali; instead, slow hydrolysis to oxindole and oxalic acid takes place. Very similar results were obtained with the 1-methyl and 1-benzyl derivatives. The structure revision suggested by Granacher and Kouniniotis [7] is thus clearly incorrect. In contrast, 3-oxindolylacetic acid is fairly readily rearranged [10] to a quinoline, and consequently hydrolysis of the esters (II; R = H, Me or benzyl, R′ = Et) must be conducted rapidly to avoid rearrangement.

Experimental

N-Methylisatin.—To a suspension of isatin (20 g.) in ethanol (300 ml.) ethanolic potassium hydroxide (100 ml.; 10%) was added portionwise during 20 min. with shaking. To the deep purple suspension, dimethyl sulphate (freshly distilled; 15 ml.) was added and the mixture was shaken for 30 min. The mixture was filtered and ethanol (340 ml.) removed from the filtrate by distillation. The residue from the filtration was added to hot water (60 ml.), the concentrated alcoholic solution was added, and the mixture heated to give a clear solution. On cooling, *N*-methylisation (17·7 g.; 80%) separated as orange needles, m. p. 134—136° (lit.,[11] m. p. 136°).

Reaction of Isatins with Ethyl Cyanoacetate.—A solution of isatin (25 g.) and ethyl cyanoacetate (20 g.) in ethanol (150 ml.) containing piperidine (0·2 ml.) was refluxed for 4 hr. After being chilled overnight, ethyl α-cyano-3-isatylideneacetate (30 g.; 73%) was filtered off and washed with a little ether. The material formed dark red needles, m. p. 196—198° (Yokayama [3] gives m. p. 202°).

Similarly, *N*-methylisatin (35·5 g.) and ethyl cyanoacetate (25 g.) yielded *ethyl α-cyano-1-methyl-3-isatylideneacetate* (47·3 g.; 84%) as dark red prisms, m. p. 188—192° (from ethanol) (Found: C, 65·6; H, 4·3; N, 11·0. $C_{14}H_{12}O_3N_2$ requires C, 65·6; H, 4·7; N, 10·9%).

Similarly, *N*-benzylisatin (5 g.) and ethyl cyanoacetate (2·5 g.) yielded the *benzyl compound* (5 g.; 75%) as dark purple needles, m. p. 166° (from ethanol) (Found: C, 72·3; H, 4·8; N, 8·7. $C_{20}H_{16}O_3N_2$ requires C, 72·3; H, 4·85; N, 8·4%).

3-Oxindolylacetonitriles.—Ethyl α-cyano-3-isatylideneacetate (30 g.) was stirred vigorously with ethyl acetate (250 ml.) and 3N-hydrochloric acid (120 ml.) while zinc dust (15 g.) was slowly added. After filtration, the organic layer was separated and dried (Na_2SO_4), and the solvent removed leaving an oil which slowly crystallised. *Ethyl α-cyano-3-oxindolylacetate* (27 g.; 90%) formed plates, m. p. 108—111° (Found: N, 11·5. $C_{13}H_{12}O_3N_2$ requires N, 11·5%).

[6] Granacher and Mahal, *Helv. Chim. Acta*, 1923, **6**, 467.
[7] Granacher and Kouniniotis, *ibid.*, 1928, **11**, 1241.
[8] Julian, Meyer, and Printy in "Heterocyclic Compounds," ed. Elderfield, New York, Interscience, 1952, vol. 3, p. 169.
[9] Horner, *Annalen*, 1941, **548**, 117.
[10] Julian, Printy, Ketcham, and Doone, *J. Amer. Chem. Soc.*, 1953, **75**, 5305.
[11] Borsche and Jacobs, *Ber.*, 1914, **47**, 361.

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Similar reduction of ethyl α-cyano-1-methyl-3-isatylideneacetate gave *ethyl α-cyano-1-methyl-3-oxindolylacetate*, prisms, m. p. 118—120° (Found: C, 65·1; H, 5·2; N, 11·1. $C_{14}H_{14}O_3N_2$ requires C, 65·1; H, 5·5; N, 10·8%).

Similar reduction of ethyl α-cyano-1-benzyl-3-isatylideneacetate gave the oxindolylacetic (II; R = benzyl, R′ = Et) as an oil.

Ethyl α-cyano-3-oxindolylacetate (10 g.) was added to boiling sodium hydroxide solution (40 ml.; 10%) under nitrogen. Boiling was continued for 4 min. and the solution was then at once chilled and acidified with hydrochloric acid. *α-Cyano-3-oxindolylacetic acid* (7·4 g.; 84%) was precipitated and formed tabular prisms, m. p. 165° with effervescence, from water (Found: C, 59·1; H, 4·3; N, 12·5. $C_{11}H_8O_3N_2,0·5H_2O$ requires C, 58·7; H, 4·0; N, 12·4%).

Similarly obtained, *α-cyano-1-methyl-3-oxindolylacetic acid* formed prisms, m. p. 115° (Found: C, 57·8; H, 4·9; N, 11·5. $C_{12}H_{10}O_3N_2,H_2O$ requires C, 58·1; H, 4·8; N, 11·3%).

Similar hydrolysis of the 1-benzyloxindolylacetate gave the corresponding acid as an oil which was decarboxylated without further purification.

α-Cyano-3-oxindolylacetic acid (5 g.) was boiled under reflux with ethylene glycol monoethyl ether (15 ml.; redistilled to remove peroxides) for 2 hr. Water (10 ml.) was added and on storage at 0° the product (3 g.) slowly crystallised. 3-Oxindolylacetonitrile formed prisms, (from ethanol) m. p. and mixed m. p. with an authentic specimen 162°.[4]

Similarly obtained, *1-methyl-3-oxindolylacetonitrile* formed prisms, m. p. 89·5—90° (from ether) (Found: C, 71·35; H, 5·2; N, 15·5. $C_{11}H_{10}ON_2$ requires C, 70·95; H, 5·4; N, 15·05%).

Similarly obtained, *1-benzyl-3-oxindolylacetonitrile* formed fine needles, m. p. 150—151° (from ethyl acetate–ethanol) (Found: C, 78·0; H, 5·2; N, 10·9. $C_{17}H_{14}ON_2$ requires C, 77·8; H, 5·4; N, 10·7%).

Oxindolylethylamines.—A solution of 3-oxindolylacetonitrile (2·2 g.) in ethanol (100 ml.) and water (20 ml.) containing concentrated hydrochloric acid (3 ml.) was hydrogenated at room temperature and atmospheric pressure over Adams's platinic oxide. Uptake of hydrogen was rapid, and was interrupted after 10% more than the calculated quantity had been absorbed (there was no break in the hydrogenation curve). After filtration, the solvent was removed leaving the crude product which was twice recrystallised from ethanol containing a little water. 2-3′-Oxindolylethylammonium chloride (1·62 g.; 60%) formed prisms, 244—246° (decomp.) with preliminary darkening (lit.,[1] m. p. 236°) (Found: C, 56·5; H, 6·1; N, 13·2. Calc. for $C_{10}H_{13}ON_2Cl$: C, 56·8; H, 6·0; N, 13·2%). The picrate had m. p. 175° (lit.,[1] m. p. 175°). The mother liquors gave a weakly positive Ehrlich reaction.

1-Methyl-3-oxindolylacetonitrile on similar reduction gave *2-(1-methyl-3-oxindolyl)ethylammonium chloride* (as IV; R = Me), m. p. 193—194° (Found: C, 57·8; H, 6·9; N, 12·4. $C_{11}H_{15}ON_2Cl$ requires C, 58·3; H, 6·6; N, 12·3%).

Similar reduction of 1-benzyl-3-oxindolylacetonitrile was unsatisfactory. Partial debenzylation appeared to occur and the resulting mixture of products was not further investigated.

Condensation of Oxindolylethylamines with Benzaldehyde.—To 2-3′-oxindolylethylammonium chloride (0·76 g.) and hydrated sodium acetate (0·5 g.) in water (3 ml.) and ethanol (20 ml.) benzaldehyde (0·38 g.) was added and the mixture refluxed for 2 hr. The solvent was removed under vacuum and the residue dissolved in dilute hydrochloric acid and extracted with ether. Sodium hydrogen carbonate was added to the aqueous layer until pH 7·3 was reached, and the precipitate was filtered off after being kept overnight at 0°. As the material was difficult to recrystallise it was characterised as *2′-phenyloxindole-3-spiro-3′-pyrrolidine picrate*, m. p. 206° from methanol (Found: C, 55·7; H, 4·1; N, 14·5. $C_{17}H_{16}ON_2,C_6N_3O_7N_3$ requires C, 56·0; H, 3·9; N, 14·2%). To 2-(1-methyl-3-oxindolyl)ethylammonium chloride (0·5 g.) in water (2 ml.) ethanolic benzaldehyde (0·22 g. in ethanol, 7 ml.) and aqueous sodium hydroxide (1·5 ml.; 10%) were added. The product slowly separated at room temperature, and was collected after 2 days. *1-Methyl-2′-phenyloxindole-3-spiro-3′-pyrrolidine* (V; R = Me) (0·6 g.) formed compact prisms, m. p. 172° (Found: C, 77·4; H, 5·85; N, 10·4. $C_{18}H_{18}ON_2$ requires C, 77·7; H, 5·6; N, 10·1%).

The material was recovered unchanged when a solution in dilute hydrochloric acid which had been boiled for 1 hr. was basified.

Reaction of α-Cyano-isatylideneacetates with Alkali.—Ethyl α-cyano-3-isatylideneacetate (1 g.) was boiled for 5 min. with sodium hydroxide solution (30 ml.; 5%). The initial dark colour changed to bright yellow. After cooling, the solution was acidified, hydrogen cyanide was then liberated and identified by smell and reaction with copper acetate–benzidine test

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paper. The yellow precipitate was twice recrystallised from acetic acid giving 3-oxindolylglyoxylic acid, m. p. 259—262° (decomp.) (lit.,[6,9] m. p. 265°), as golden-yellow plates (Found: C, 58·7; H, 3·7; N, 7·3. Calc. for $C_{10}H_7O_4N$: C, 58·5; H, 3·4; N, 6·8%). The ethyl ester (ethanol–sulphuric acid), m. p. 185—187°, was identical (mixed m. p.) with a specimen prepared by Horner's [9] method. Brief alkaline hydrolysis of the ester regenerated the original acid: the ultraviolet spectra of the ester and acid were almost superposable.

Similarly, ethyl α-cyano-1-methyl-3-isatylideneacetate gave *1-methyl-3-oxindolylglyoxylic acid*, yellow plates, m. p. 238° (Found: C, 60·05; H, 3·85; N, 6·5. $C_{11}H_9O_4N$ requires C, 60·3; H, 4·1; N, 6·4%), and the benzyl compound gave *1-benzyl-3-oxindolylglyoxylic acid*, yellow prisms, m. p. 236° (Found: C, 68·8; H, 4·5; N, 4·7. $C_{17}H_{13}O_4N$ requires C, 69·1; H, 4·4; N, 4·7%).

The authors thank Dr. J. W. Cornforth, F.R.S., for a specimen of 3-oxindolylacetonitrile.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, April 28th*, 1958.]

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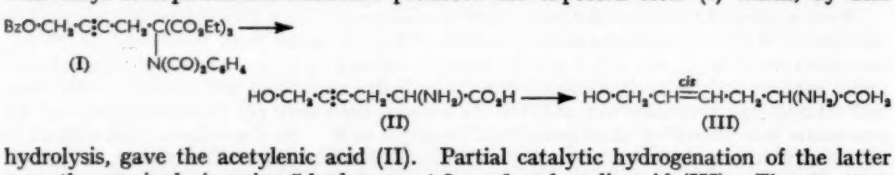
729. *The Synthesis of* DL-*Baikiain.*

By N. A. DOBSON and R. A. RAPHAEL.

The synthesis of baikiain (1 : 2 : 3 : 6-tetrahydropyridine-2-carboxylic acid) from but-2-yne-1 : 4-diol is described.

THE amino-acid baikiain (XIII) was first isolated from the heartwood of Rhodesian teak (*Baikiaea plurijuga*) by King, King, and Warwick [1] and shown by degradation to be L-1 : 2 : 3 : 6-tetrahydropyridine-2-carboxylic acid. Biogenetically it has been suggested as an intermediary between the 4- and 5-hydroxypipecolic acid.[2] An attempted synthesis of baikiain [1] led only to an impure concentrate in which the required compound was shown by paper chromatography to be present in small amount. Alternative synthetic routes based on acetylenic intermediates were therefore examined.

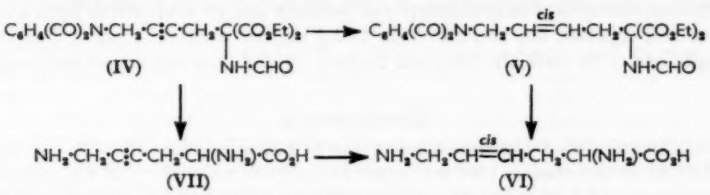
The well-known ready cyclisation of 1 : 5-amino-alcohols to the corresponding piperidines [3] suggested that an analogous dehydration of *cis*-1-amino-5-hydroxypent-3-ene-1-carboxylic acid (III) would proceed with ease to yield baikiain. Accordingly the former compound was synthesised in the following manner. Condensation of 1-benzoyloxy-4-bromobut-2-yne (prepared from but-2-yne-1 : 4-diol by Fraser and Raphael's method [4]) with ethyl sodiophthalimidomalonate produced the expected ester (I) which, by acid



hydrolysis, gave the acetylenic acid (II). Partial catalytic hydrogenation of the latter gave the required *cis*-amino-5-hydroxypent-3-ene-1-carboxylic acid (III). The structure of this product was confirmed by its hydrogenation to the known 1-amino-5-hydroxypentane-1-carboxylic acid.[5] All attempts to cyclise the acid (III) by acidic or basic dehydrating agents proved fruitless. That its zwitterion nature was not the prime cause was shown by the similar resistance to dehydration of the methyl ester. The reason is indeed obscure, in view of the successful closely analogous ring closure of 1-amino-4-hydroxybutane-1-carboxylic acid to proline.[6]

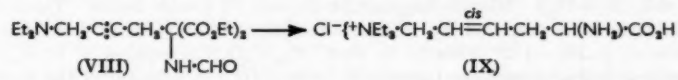
[1] King, King, and Warwick, *J.*, 1950, 3590.
[2] Witkop, *Chem. Soc. Special Publ.* No. 3, 1955, p. 81.
[3] *E.g.*, Woods and Sanders, *J. Amer. Chem. Soc.*, 1946, **68**, 2111.
[4] Fraser and Raphael, *J.*, 1955, 4280.
[5] Gaudry, *Canad. J. Res.*, 1948, **26**, *B*, 387.
[6] Plieninger, *Chem. Ber.*, 1950, **83**, 271.

Another, though less ready, synthesis of piperidine systems, involves the elimination of ammonia from 1 : 5-diamines.[7] The elaboration of the requisite diamino-acid (VI) started from 1 : 4-dichlorobut-2-yne which with one equivalent of potassium phthalimide in dimethylformamide gave a low yield of 1-chloro-4-phthalimidobut-2-yne. Interaction



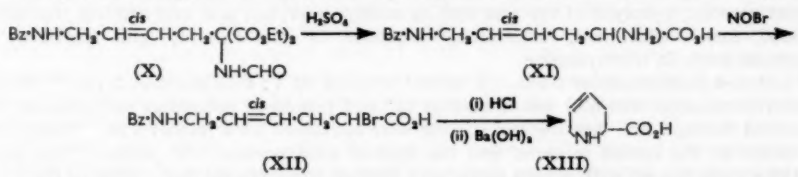
with ethyl sodioformamidomalonate then produced the expected acetylenic ester (IV) which, by partial catalytic hydrogenation, followed by acid hydrolysis of the resulting *cis*-ester (V), gave the required *cis*-1 : 5-diaminopent-3-ene-1-carboxylic acid (VI) best isolated as its crystalline sulphate. The structure was confirmed by catalytic hydrogenation to DL-lysine. That no stereomutation of the *cis*-ethylene had occurred during the relatively drastic hydrolysis was confirmed by hydrolysis of the ester (IV) to the acetylenic diamino-acid (VII) and partial catalytic hydrogenation of this to the same product (VI). Later it was found that the acid (VI) could be obtained more easily in much higher yield by using 1-benzamido-4-chlorobut-2-yne instead of the phthalimido-derivative; this starting material was readily made by treating 1 : 4-dichlorobut-2-yne with hexamine [8] and benzoylating the resulting 1-amino-4-chlorobut-2-yne. Attempts to cyclise the diamino-acid (VI) to baikiain by removing the elements of ammonia failed.

In a variant of this approach the quaternary ammonium chloride (IX) was obtained by interaction of formaldehyde, diethylamine, and ethyl α-formamido-α-propargylmalonate to give the ester (VIII), followed by partial catalytic hydrogenation, quaternisation, and acid-hydrolysis. Treatment of this quaternary salt (IX) with hot alkali did indeed result in the elimination of triethylamine but no baikiain could be detected in the product.



The successful synthesis arose from the observation that, under carefully controlled conditions, selective hydrolysis of diethyl *cis*-5-benzamido-1-formamidopent-3-ene-1 : 1-dicarboxylate (X) to *cis*-1-amino-5-benzamidopent-3-yne-1-carboxylic acid (XI) could be effected in high yield by sulphuric acid. Surprisingly the *free* amino-acid (XI) crystallised from the acid reaction medium.

The free amino-group in (XI) was smoothly replaced by treatment with nitrosyl bromide, to give the crystalline bromo-acid (XII). Hydrolysis of the benzamido-group, followed by base-catalysed elimination of hydrogen bromide, then furnished a crystalline



product identical with baikiain in melting point, chromatographic behaviour, ninhydrin coloration, and infrared absorption. The *N*-benzoyl derivatives of the synthetic and the

[7] Elderfield, "Heterocyclic Compounds," Vol. I, Chapman and Hall Ltd., London 1950, p. 642 *et seq.*

[8] Marszak-Fleury, *Compt. rend.*, 1955, **241**, 752.

natural product were also identical in m. p., mixed m. p., and infrared spectra. The *N*-benzoyl derivative was also obtained by the direct cyclisation of the benzamido-acid (XII) with barium hydroxide. The absence of depression in melting point in mixtures of the synthetic DL- and the natural L-baikiain and of the corresponding derivatives seems to indicate that the optical enantiomorphs of baikiain and its derivatives form a continuous series of mixed crystals, the racemic form being neither a eutectic nor a true compound. The overall yield of DL-baikiain from but-2-yne-1 : 4-diol in seven stages was over 6%.

EXPERIMENTAL

Diethyl 5-Benzoyloxy-1-phthalimidopent-3-yne-1 : 1-dicarboxylate (I).—To a solution of sodium (2·22 g.) in dry ethanol (200 ml.) ethyl phthalimidomalonate [9] (29·4 g.) was added and the mixture heated for 1 hr. The solvent was taken off under reduced pressure and the ethanol of crystallisation removed by heating the residual solid for 1 hr. at 150°/0·5 mm. The sodio-derivative thus formed was finely powdered and suspended in dry toluene (500 ml.). 1-Benzoyloxy-4-bromobut-2-yne [4] (20·4 g.) was added and the mixture heated under reflux for 72 hr. After hot filtration through charcoal the solution was acidified with acetic acid (2 ml.). The cooled solution was washed with N-sulphuric acid and sodium hydrogen carbonate solution, dried ($MgSO_4$), and evaporated, to give a semi-solid residue which was dissolved in ethanol (40 ml.) and cooled to −15°. The almost pure *ester* (I) (26·5 g., 69%) crystallised; an analytical sample crystallised from *n*-butyl ether as plates, m. p. 63—64° (Found: C, 65·2; H, 4·7. $C_{24}H_{23}O_6N$ requires C, 65·4; H, 4·8%).

1-Amino-5-hydroxypent-3-yne-1-carboxylic Acid (II).—The ester (I) (6·7 g.) was heated in ethanol (50 ml.) and 12N-hydrochloric acid (10 ml.) under reflux for 9 hr. with further additions of 12N-hydrochloric acid at 30-minute intervals (10 × 10 ml.). The filtered mixture was reduced to 5 ml. under reduced pressure and the hygroscopic amino-acid hydrochloride precipitated by addition of acetone (150 ml.). This was dissolved in a little water and treated with ion-exchange resin (Amberlite IR-4B) until the solution was neutral. Evaporation of the filtrate under reduced pressure gave a residue of the crude amino-hydroxy-acid contaminated with a little glycine; this impurity was conveniently removed by sublimation at 180°/10^{-5} mm. Crystallisation of the residue from methanol furnished the pure *amino-hydroxy-acid* (II) as needles (1·5 g., 75%), m. p. 192° (decomp.) (Found: C, 50·0; H, 6·5; N, 9·3. $C_6H_9O_3N$ requires C, 50·3; H, 6·3; N, 9·7%). Microhydrogenation showed 2·2 double bonds. The corresponding *3-phenyl-2-thiohydantoin* prepared by Edman's technique [10] crystallised from water in pale-yellow prisms, m. p. 171—172° (Found: N, 10·8. $C_{13}H_{12}O_2N_2S$ requires N, 10·8%).

cis-*1-Amino-5-hydroxypent-3-ene-1-carboxylic Acid* (III).—A solution of the acetylenic acid (II) (1·086 g.) in water (20 ml.) was catalytically hydrogenated (10% palladium–charcoal) until 1 mol. of hydrogen had been absorbed. Filtration, evaporation, and crystallisation of the residue from methanol gave the ethylenic *acid* (III), m. p. 227° (decomp.) (Found: C, 49·6; H, 7·9; N, 9·7. $C_6H_{11}O_3N$ requires C, 49·6; H, 7·6; N, 9·7%). Complete hydrogenation of this in water using Adams catalyst gave 1-amino-5-hydroxypentane-1-carboxylic acid, crystallising from water in needles, m. p. 254—260° (decomp.) [lit.,[5] m. p. 260—262° or 245—248° (decomp.) depending on the rate of heating]. The phenylureido-derivative crystallised from water in plates, m. p. 138° (lit.,[5] m. p. 141°) (Found: N, 10·8. Calc. for $C_{13}H_{18}O_4N_2$: N, 10·5%).

The following methods of converting the amino-hydroxy-acid (III) into baikiain were tried without success; pyrolysis of the acid and its methyl ester, hot acid and alkaline treatment of the acid, fusion with urea, ammonium carbonate, or zinc chloride, and treatment with phosphoric oxide in triethylamine.

1-Chloro-4-phthalimidobut-2-yne.—A stirred solution of 1 : 4-dichlorobut-2-yne [11] (57 g.) in dimethylformamide (350 ml.) was heated at 95° and powdered potassium phthalimide (88 g.) was added during 2 hr.; heating and stirring were continued for a further 8 hr. Water (1·5 l.) was added to the cooled mixture, and the filtered solid washed with water. This product (*ca.* 160 g.) was heated with glacial acetic acid (300 ml.) and filtered hot. Most of the 1 : 4-diphthalimidobut-2-yne [12] remained undissolved and was filtered off; the cooled solution

[9] Osterberg, *Org. Synth.*, Coll. Vol. I, 2nd edn., p. 271.
[10] Edman, *Acta Chem. Scand.*, 1950, **4**, 277.
[11] Johnson, *J.*, 1946, 1009.
[12] Fraser and Raphael, *J.*, 1952, 226.

deposited more of this compound. To the filtrate water (1 l.) was added and the precipitated solid filtered off and crystallised from ethanol; the pure *1-chloro-4-phthalimidobut-2-yne* (30—40%) formed pale yellow needles, m. p. 116—117° (Found: C, 62·0; H, 3·4. $C_{12}H_8O_2NCl$ requires C, 61·7; H, 3·4%).

Diethyl 1-Formamido-5-phthalimidopent-3-yne-1 : 1-dicarboxylate.—Ethyl formamidomalonate (16·3 g.) was added to ethanol (300 ml.) in which sodium (1·84 g.) had been dissolved, and the solution warmed at 50° for 1 hr. 1-Chloro-4-phthalimidobut-2-yne (18·7 g.) was added and the stirred mixture heated under reflux for 14 hr. The volume was reduced to 100 ml. and acetic acid (1 ml.) added. Addition of water precipitated the crude product as an oil which became semi-solid after some time at 0°. Crystallisation proved difficult and tedious but the pure *ester* (IV) (30—40%) was finally obtained as needles, m. p. 122° [from light petroleum (b. p. 60—80°)–ethanol (9 : 1)] (Found: C, 60·1; H, 4·8. $C_{20}H_{20}O_7N_2$ requires C, 60·0; H, 5·0%). The sodium hydride method (see below) gave a lower yield.

Diethyl cis-*1-Formamido-5-phthalimidopent-3-ene-1 : 1-dicarboxylate* (V).—A solution of the acetylenic ester (IV) (7·1 g.) in ethyl acetate (150 ml.) was subjected to partial catalytic hydrogenation in the presence of Lindlar catalyst [13] (2 g.). Removal of catalyst and solvent, followed by crystallisation of the residue from light petroleum (b. p. 60—80°)–ethanol (9 : 1), gave the *cis*-ethylenic *ester* (6·6 g., 92%) as needles, m. p. 110° (Found: C, 59·5; H, 5·3. $C_{20}H_{22}O_7N_2$ requires C, 59·7; H, 5·5%).

Dihydrochloride of 1 : 5-Diaminopent-3-yne-1-carboxylic Acid (VII).—The acetylenic ester (IV) (5 g.) was heated under reflux for 6 hr. with 6N-hydrochloric acid (40 ml.). The volume was reduced to 10 ml. under reduced pressure and the phthalic acid was filtered off. After further concentration of the filtrate to 3 ml. the crude product was precipitated by addition of acetone. Crystallisation from aqueous ethanol (90%) gave the *diamino-acid dihydrochloride* (2·04 g., 76%) as needles, m. p. 192—194° (decomp.) with preliminary softening at 120—140° (Found: C, 33·7; H, 5·65; N, 13·05. $C_6H_{10}O_2N_2,2HCl$ requires C, 33·7; H, 5·85; N, 13·05%). The NN′-*dibenzoyl derivative* prepared by the Schotten–Baumann procedure crystallised from aqueous ethanol as prisms, m. p. 176° (Found: N, 8·2. $C_{20}H_{18}O_4N_2$ requires N, 8·0%).

Salts of cis-*1 : 5-Diaminopent-3-ene-1-carboxylic Acid* (VI).—(*a*) The *cis*-ethylenic ester (V) (1·6 g.) was heated under reflux for 6 hr. with dilute sulphuric acid (2 ml. of concentrated acid and 17 ml. of water). The volume was then reduced under reduced pressure to 4 ml.; cooling to 0° precipitated phthalic acid which was filtered off. Ethanol (75 ml.) was added to the filtrate and the solution set aside at −5° for 48 hr. The resulting solid was purified by dissolution in the minimum quantity of hot water and addition of boiling ethanol until a turbidity was formed. Slow cooling then gave the *diamino-acid sulphate* (0·57 g., 59%) as feathery needles, m. p. 235° (decomp.) (Found: C, 29·8; H, 6·1; N, 11·7. $C_6H_{12}O_2N_2,H_2SO_4$ requires C, 29·8; H, 5·8; N, 11·6%). The NN′-*dibenzoyl derivative*, prepared by the Schotten–Baumann procedure, yielded prisms, m. p. 180—181° (from water) (Found: N, 8·1. $C_{20}H_{20}O_4N_2$ requires N, 7·95%). Complete hydrogenation of the sulphate in water over palladium–charcoal, followed by benzoylation, gave *NN′*-dibenzoyl-DL-lysine, crystallising from aqueous acetone (90%) in needles, m. p. 145—146° (lit.,[14] m. p. 145—146°).

(*b*) A solution of the dihydrochloride (3·93 g.) of the acetylenic diamino-acid (VII) in water (40 ml.) was catalytically hydrogenated over 10% palladium–charcoal (1 g.). After absorption of 1 mol. of hydrogen and removal of catalyst the filtrate was reduced to 5 ml. under reduced pressure. Addition of acetone (100 g.) then precipitated an oil which solidified on being warmed with ethanol. Crystallisation from aqueous ethanol (95%) gave the *diamino-acid monohydrochloride* (1·57 g., 53%) as prisms, m. p. 257—258° (decomp.) (Found: C, 39·9; H, 7·0; N, 15·6. $C_6H_{12}O_2N_2,HCl$ requires C, 39·9; H, 7·25; N, 15·5%). Addition of acetone to the crystallisation mother-liquors precipitated an extremely hygroscopic solid (1 g.) which was shown by a chlorine estimation to be mainly composed of the corresponding dihydrochloride. This hygroscopic dihydrochloride was also obtained by hydrochloric acid hydrolysis of the ethylenic ester (V). Both hydrochlorides gave the same *NN′*-dibenzoyl derivative identical with that prepared from the sulphate as in (*a*), and both were converted into this sulphate by successive treatment with ammonia and sulphuric acid.

Attempts to cyclise the diamino-acid salts to baikiain by methods similar to those detailed above for the corresponding hydroxyamino-acid were unsuccessful. In addition, treatment of

[13] Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446.
[14] von Braun, *Ber.*, 1909, **42**, 845.

the diamino-acid monohydrochloride with nitrosyl chloride under conditions similar to those used to convert lysine into pipecolic acid [15] gave no detectable trace of baikiain.

Diethyl cis-5-*Diethylamino*-1-*formamidopent*-3-*ene*-1 : 1-*dicarboxylate*.—A solution of ethyl α-formamido-α-propargylmalonate [16] (8 g.) and diethylamine (3 g.) in dioxan (10 ml.) was heated with paraformaldehyde (1·5 g.) in a sealed tube by steam for 12 hr. The dioxan was removed under reduced pressure, the residue dissolved in ether, and the solution filtered from a small amount of gum. The ether was evaporated off and the residue heated at 100° under a high vacuum for 30 min. On cooling, the residue solidified and crystallised from benzene–light petroleum (b. p. 60—80°), to give *diethyl* 5-*diethylamino*-1-*formamidopent*-3-*yne*-1 : 1-*dicarboxylate* (VIII) (68%) as prisms, m. p. 70°, readily soluble in dilute acid (Found: C, 58·8; H, 7·9; N, 9·0. $C_{14}H_{24}O_5N_2$ requires C, 58·9; H, 8·0; N, 8·6%). This material was partially catalytically hydrogenated in ethyl acetate with 10% palladium–charcoal. Removal of catalyst and solvent gave a gum which slowly solidified. Crystallisation from benzene–light petroleum (b. p. 60—80°) gave the cis-*ester* as cream needles, m. p. 73—74° (Found: C, 58·6; H, 8·7; N, 8·3. $C_{14}H_{26}O_5N_2$ requires C, 58·5; H, 8·6; N, 8·5%). Heating this ester with ethanolic ethyl iodide gave the corresponding quaternary salt which was then hydrolysed by hot hydrochloric acid to the hygroscopic *N*-(5-amino-5-carboxypent-2-*cis*-enyl)triethylammonium chloride (IX). This product was unaffected by warm 0·5N- or N-alkali but 50% aqueous sodium hydroxide at 100° caused rapid evolution of triethylamine. Paper-chromatographic investigation of the product showed no trace of baikiain.

1-*Benzamido*-4-*chlorobut*-2-*yne*.—Hexamine (14 g.), 1 : 4-dichlorobut-2-yne (12·3 g.), and chloroform (100 ml.) were heated under reflux for 20 min., then cooled. The hexamine complex was filtered off; evaporation of the filtrate to smaller bulk gave a second crop (total yield, 93%). The product formed white irregular crystals, m. p. 200—210° (with discoloration after 185°) (Found: N, 20·6. Calc. for $C_{10}H_{16}N_4Cl_2$: N, 20·9%). A solution of the complex (128 g.) in ethanol (960 ml.) was shaken for 24 hr. at room temperature with concentrated hydrochloric acid (170 ml.). The precipitate of ammonium chloride was filtered off and the filtrate concentrated under reduced pressure until crystallisation was incipient. Addition of dry ether then precipitated the hydrochloride (55 g., 74%) of 1-amino-4-chlorobut-2-yne as white plates; purification was attained by dissolution in the minimum quantity of ethanol and precipitation by ether (Found: C, 34·0; H, 5·2; N, 9·7. Calc. for C_4H_6NCl,HCl: C, 34·3; H, 5·05; N, 10·0%). The amine hydrochloride (120 g.) was dissolved in water (500 ml.). 30% Sodium hydroxide solution (2·5 mols.) was then added, followed immediately by benzoyl chloride, with vigorous shaking and cooling. Care was taken that the mixture remained alkaline throughout the reaction. After 15 minutes' further shaking the initially oily precipitate solidified and was filtered off, washed with water, and dried in a vacuum-desiccator. Crystallisation from benzene–*cyclo*hexane (1 : 3) gave 1-*benzamido*-4-*chlorobut*-2-*yne* (147 g., 82%) as white plates, m. p. 95—96° (Found: C, 63·4; H, 4·75; N, 6·5. $C_{11}H_{10}ONCl$ requires C, 63·4; H, 4·85; N, 6·7%).

Diethyl 5-*Benzamido*-1-*formamidopent*-3-*yne*-1 : 1-*dicarboxylate*.—To a suspension of sodium hydride (3·84 g.) in dry benzene (10 ml.) was added a solution of ethyl formamidomalonate (29·2 g.) in benzene (50 ml.) and the mixture stirred at gentle reflux for 30 min. A solution of 1-benzamido-4-chlorobut-2-yne (29·2 g.) in benzene (50 ml.) was then added and refluxing continued for 5 hr. A small quantity of ethanol was then added to the cooled solution to decompose excess of hydride, followed by water (100 ml.). Sometimes the product crystallised almost immediately; where this did not occur the benzene layer was separated and evaporated to half its bulk. The separated *ester* (74%) was filtered off and crystallised from benzene as needles, m. p. 134° (Found: C, 61·3; H, 5·95; N, 7·6. $C_{19}H_{22}O_6N_2$ requires C, 61·0; H, 5·9; N, 7·5%).

Diethyl cis-5-*Benzamido*-1-*formamidopent*-3-*ene*-1 : 1-*dicarboxylate* (X).—A solution of the corresponding acetylenic ester (7·5 g.) in ethyl acetate (150 ml.) was partially catalytically hydrogenated with 10% palladium–charcoal (0·5 g.). After 1 mol. of hydrogen had been absorbed, catalyst and solvent were removed to give the product which rapidly solidified. Crystallisation was best effected by dissolution in a small quantity of warm benzene followed by addition of 5 volumes of dry ether. At 0° the ethylenic *ester* (X) (93%) crystallised as needles or rods, m. p. 85° (Found: C, 60·5; H, 6·15; N, 7·65. $C_{19}H_{24}O_6N_2$ requires C, 60·6; H, 6·4;

[15] Schiedt and Hoss, *Z. physiol. Chem.*, 1957, **308**, 179.
[16] Gerston, Shapira, Meek, and Dittmar, *J. Amer. Chem. Soc.*, 1954, **76**, 3484.

N, 7·45%). Complete hydrogenation of a small quantity of this material gave the corresponding saturated *ester*, prisms, m. p. 83° (from benzene) (Found: C, 60·4; H, 6·75; N, 7·3. $C_{19}H_{26}O_6N_2$ requires C, 60·3; H, 6·9; N, 7·4%). Acid hydrolysis of the latter, followed by benzoylation, gave *NN'*-dibenzoyl-DL-lysine, m. p. and mixed m. p. 143—144°.

cis-1-*Amino-5-benzamidopent-3-ene-1-carboxylic Acid* (XI).—The *cis*-ester (X) (5·5 g.) was heated under reflux with dilute sulphuric acid (15 g. of concentrated acid and 100 ml. of water) for 2·5 hr. and the solution then chilled. The precipitated benzoic acid was filtered off and the filtrate extracted with ether. The total amount of benzoic acid thus obtained showed that there had been about 18% hydrolysis of the benzoyl group. The bulk of the sulphuric acid in the solution was removed by the addition of 95% of the theoretical amount of warm barium hydroxide solution. The acidic filtrate was evaporated to small bulk under reduced pressure and the product (2·5 g., 68%) crystallised from the chilled concentrate. The *amino-acid* (XI) crystallised from water in plates, m. p. 234° (Found: C, 62·6; H, 6·3; N, 10·9. $C_{13}H_{16}O_3N_2$ requires C, 62·9; H, 6·5; N, 11·3%). The *benzoyl derivative* crystallised from water in prisms, m. p. 183—185° (Found: C, 68·4; H, 5·7; N, 7·95. $C_{20}H_{20}O_4N_2$ requires C, 68·2; H, 5·7; N, 7·95%). Catalytic hydrogenation of this derivative gave *NN'*-dibenzoyl-DL-lysine.

cis-1-*Bromo-5-benzamidopent-3-ene-1-carboxylic Acid* (XII).—To a chilled (0°) solution of the *cis*-amino-acid (XI) (1·24 g.) in 2·5N-sulphuric acid (10 ml.) containing potassium bromide (2 g.), sodiium nitrite (0·55 g.) was added in portions during 30 min. The precipitated gum was isolated with ether and slowly solidified on being set aside. Crystallisation from benzene gave the *bromo-acid* (XII) (58%) as needles, m. p. 103—104° (Found: C, 49·8; H, 4·45; N, 4·7. $C_{13}H_{14}O_3NBr$ requires C, 50·0; H, 4·5; N, 4·5%).

DL-*Baikiain* (XIII).—The above bromo-acid (XII) (0·6 g.) was heated under reflux for 12 hr. with 10% hydrochloric acid (10 ml.). The mixture was evaporated under reduced pressure and the residue washed with dry ether. It was then dissolved in a little water and neutralised with ion-exchange resin (Amberlite IR-4B). After removal of the resin the filtrate was treated with N-barium hydroxide (10 ml.) and warmed at 50° for 30 min. A slight excess of 2N-sulphuric acid was then added, the barium sulphate removed, and the filtrate neutralised with resin (Amberlite IR-4B). The neutral solution was evaporated to dryness and the resulting solid dissolved in methanol and reprecipitated with acetone. Crystallisation from methanol gave DL-*baikiain* (51%) as prisms, m. p. 273—274° (decomp.) undepressed on admixture with authentic L-baikiain [m. p. 273—274° (decomp.)]. The infrared absorption curves of the two compounds in potassium bromide discs were identical. Paper chromatograms of the natural and the synthetic compound, with aqueous phenol as the mobile phase, gave spots identical in position, shape, and ninhydrin coloration. Benzoylation of the synthetic amino-acid gave *N-benzoyl*-DL-*baikiain*, crystallising from ethyl acetate in prisms, m. p. 179—180°, undepressed on admixture with *N*-benzoyl-L-baikiain, m. p. 178—179° (Found: C, 67·6; H, 5·4; N, 5·75. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·65; N, 6·05%). The same derivative was obtained (23%) by direct dehydrobromination of the bromo-acid (XII) with barium hydroxide. Hydrolysis of the benzoyl derivative with hot 20% hydrochloric acid gave DL-baikiain hydrochloride (87%), m. p. 264° (decomp.) (from ethanol–ether). The m. p. was undepressed by admixture with L-baikiain hydrochloride [m. p. 264° (decomp.)].

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THE UNIVERSITY, GLASGOW, W.2.
THE QUEEN'S UNIVERSITY, BELFAST.

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730. *The Chemistry of Certain Acyloxyboron Compounds and Boron Chelates.*

By W. Gerrard, M. F. Lappert, and R. Shafferman.

Eight acyloxyboron compounds have been obtained, four methods being used. The compounds hydrolysed readily and some decomposed with elimination of carboxylic anhydride.

The present paper relates to the preparation, characterisation, and selected reactions of acyloxyboron compounds of types (I) and (II) (R = Me or CF_3), and to certain new ethoxycarbonyl-substituted boron esters. Existence of only one compound of type (I) has previously been established with certainty, namely, acetyl diethylboronite,[1] $Et_2B{\cdot}OAc$,

(I) $>B{\cdot}O{\cdot}COR$ $\qquad$ $R{\cdot}CO{\cdot}O{\cdot}B(-)B{\cdot}O{\cdot}COR$ (II)

prepared from triethylboron and acetic acid. The so-called " acyl borates " had been thought to be triacyl borates,[2] $(R{\cdot}CO{\cdot}O)_3B$, but recent evidence[3] confirms an earlier suggestion[4] that they are tetra-acyl diborates, $[(R{\cdot}CO{\cdot}O)_2B]_2O$. The only other acyloxyboron compounds hitherto reported[5,6] are of type (II) $(AcO{\cdot}BY)_2O$ (Y = Cl or Bu^n). Certain trifluoroacetoxyboron compounds of indefinite compositon have been mentioned in a recent patent.[7]

Tristrifluoroacetyl borate, $(CF_3{\cdot}CO{\cdot}O)_3B$, diacetyl phenylboronate, $(AcO)_2BPh$, and acyl di-*n*-butylboronites, $R{\cdot}CO{\cdot}O{\cdot}BBu^n_2$, were each obtained from the appropriate boron chloride and carboxylic acid by elimination of hydrogen chloride. Under similar conditions boron trichloride and acetic acid gave the diborate,[5] whereas with phenylboron dichloride and trifluoroacetic acid dephenylation (reaction 1) was observed (for other dephenylations see ref. 8). Similar dephenylation occurred when diphenylboron chloride was treated with acetic acid [$Cl{\cdot}BPh_2 + 2AcOH \longrightarrow (AcO)_2B{\cdot}Ph + HCl + C_6H_6$]. With the *n*-butoxyboron chlorides and acetic acid, the products isolated are presumed to have been formed by decomposition of intermediate *n*-butoxyboron acetates (reactions 2 and 3).

$$Cl_2B{\cdot}Ph + 3CF_3{\cdot}CO_2H \longrightarrow (CF_3{\cdot}CO{\cdot}O)_3B + C_6H_6 + 2HCl \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$3Cl_2B{\cdot}OBu^n + 6AcOH \xrightarrow{-6HCl} 3[(AcO)_2B{\cdot}OBu^n] \longrightarrow [(AcO)_2B]_2O + B(OBu^n)_3 + Ac_2O \quad . \quad . \quad (2)$$

$$6Cl{\cdot}B(OBu^n)_2 + 6AcOH \xrightarrow{-6HCl} 6[AcO{\cdot}B(OBu^n)_2] \longrightarrow [(AcO)_2B]_2O + 4B(OBu^n)_3 + Ac_2O \quad . \quad (3)$$

Bistrifluoroacetyl phenylboronate, $(CF_3{\cdot}CO{\cdot}O)_2BPh$, and trifluoroacetyl diphenylboronite, $CF_3{\cdot}CO{\cdot}O{\cdot}BPh_2$, were obtained from the phenylboron chlorides and sodium trifluoroacetate with elimination of sodium chloride.

The compound $[(CF_3{\cdot}CO{\cdot}O)BBu^n]_2O$ was obtained from di-*n*-butylboronous anhydride $(Bu^n_2B)_2O$ (1 mol.), and trifluoroacetic acid (2 mols.) by elimination of *n*-butane (2 mols.). Tetrakistrifluoroacetyl diborate $[(CF_3{\cdot}CO{\cdot}O)_2B]_2O$ was prepared from tristrifluoroacetyl borate by sublimation *in vacuo*, trifluoroacetic anhydride being the other product.

It was necessary to develop a technique for estimating acetic acid and boric acid, in some cases in presence of hydrogen peroxide [used to oxidise $Bu^n{\cdot}B(OH)_2$ and $Bu^n_2B{\cdot}OH$ to boric acid]. By potentiometric titration it was established that a mixture of boric acid, hydrogen peroxide, and mannitol has pH 6·8 (in the absence of hydrogen peroxide,

[1] Meerwein and Sönke, *J. prakt. Chem.*, 1937, **147**, 251.
[2] Pictet and Geleznoff, *Ber.*, 1903, **36**, 2219.
[3] Gerrard and Wheelans, *Chem. and Ind.*, 1954, 758; Gerrard and Mooney, *ibid.*, 1958, 227; Hayter, Laubengayer, and Thomson, *J. Amer. Chem. Soc.*, 1957, **79**, 4243.
[4] Dimroth, *Annalen*, 1926, **446**, 97.
[5] Gerrard and Wheelans, *J.*, 1956, 4296.
[6] Gerrard, Lappert, and Shafferman, *J.*, 1957, 3828.
[7] Muetterties, U.S.P. 2,782,233/1957.
[8] Abel, Gerrard, and Lappert, *J.*, 1957, 5051; *J.*, 1958, 1451.

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pH 8·2) and the procedure now recommended for analysing a mixture of a carboxylic acid and boric acid is to titrate in the presence of hydrogen peroxide to Bromothymol Blue (pH 6·0—7·6) with sodium hydroxide, first in the absence ($R{\cdot}CO_2H$), then in the presence [$B(OH)_3$], of mannitol. We also regard this method as the best available for estimating boron in alkylboronic acids, $R{\cdot}B(OH)_2$, dialkylboronous acids, $R_2B{\cdot}OH$, and their derivatives.

All the acyloxyboron compounds were hydrolysed by cold water to the carboxylic acid and boric, boronic, or boronous acids. This was established for acetyl di-*n*-butylboronite by isolation of acetic acid and di-*n*-butylboronous anhydride (formed by dehydration of $HO{\cdot}BBu^n_2$) and for the other compounds by analysis.

Replacement of acyloxy- by alkoxy-groups has been made use of for preparing orthoborates from tetra-acetyl diborate, and such replacement has now been further demonstrated by converting trifluoroacetyl di-*n*-butylboronite into (+)-1-methylheptyl di-*n*-butylboronite by reaction with (+)-octan-2-ol.

The acyloxyboron compounds may be regarded as mixed anhydrides of carboxylic and boric or substituted boric acids and thus redistribution might be expected; such a reaction involving tristrifluoroacetyl borate has been mentioned above. The only other compounds which showed a similar tendency were acetyl di-*n*-butylboronite (which, however, it was possible to distil without change in analysis) and diacetyl phenylboronate; in these compounds the presence of acetic anhydride was detected spectroscopically [9] and in one case by gas–liquid chromatography.

Reaction of acetyl di-*n*-butylboronite with either of the two carboxylic acids resulted in the elimination (as *n*-butane) of only one butyl group.

In view of the fact that acyloxyboron compounds are frequently chelated as a result of co-ordination of the carbonyl-oxygen atom with the boron atom,[9] certain potentially chelated ethoxycarbonyl-substituted boron esters were prepared. These were the esters $EtO_2C{\cdot}CH{:}CMe{\cdot}O{\cdot}BR_2$ (R = Bu and Ph), and $EtO_2C{\cdot}CHMe{\cdot}O{\cdot}BBu^n_2$, obtained from the appropriate chloride, R_2BCl, and ethyl acetoacetate or ethyl lactate, hydrogen chloride being eliminated.

With regard to substitution of a hydrocarbon radical by an acyloxy-group (*e.g.*, reaction 1), it appears that: (1) dearylation is easier than dealkylation, (2) the propensity for dearylation increases with the number of aryl groups attached to boron, and (3) dearylation is encouraged by increasing acid strength, $CF_3{\cdot}CO_2H > AcOH$.

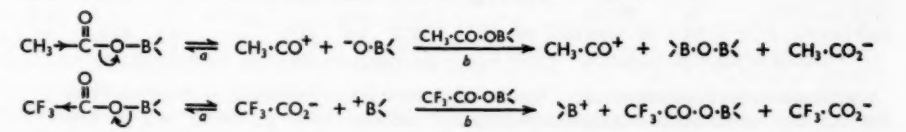
Three types of disproportionation in acyloxyboron compounds have been noted [(4), (5), (6)] and this tendency is greater when R = Me than when $R = CF_3$: [9]

$$2(R{\cdot}CO{\cdot}O)_3B \longrightarrow [(R{\cdot}CO{\cdot}O)_2B]_2O + (R{\cdot}CO)_2O \quad (4)$$

$$3(R{\cdot}CO{\cdot}O)_3B{\cdot}R' \longrightarrow (R'BO)_3 + 3(R{\cdot}CO)_2O \quad (5)$$

$$2R{\cdot}CO{\cdot}O{\cdot}BR'_2 \longrightarrow (R'_2B)_2O + (R{\cdot}CO)_2O \quad (6)$$

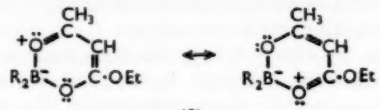
The greater stability of the trifluoroacetates than of the acetates has also been noted with mixed carboxylic acid anhydrides,[10,11] and the present results may be explained by postulating reversible dissociations similar to those put forward for the mixed anhydrides,[11,12] with subsequent competing reactions [(*a*) and (*b*)].



[9] Duncanson, Gerrard, Lappert, Pyszora, and Shafferman, following paper.
[10] Emmons, McCallum, and Ferris, *J. Amer. Chem. Soc.*, 1953, **75**, 6047; Randles, Tatlow, and Tedder, *J.*, 1954, 436.
[11] Bourne, Stacey, Tatlow, and Worral, *J.*, 1954, 2006.
[12] Emery and Gold, *J.*, 1950, 1443, 1447.

The optical activity data on the alcoholysis of trifluoroacetyl di-*n*-butylboronite show that alkyl–oxygen fission is not involved.

It has been shown that 1-ethoxycarbonylethyl di-*n*-butylboronite is not chelated, whereas chelation occurs with 2-ethoxycarbonyl-1-methylvinyl di-*n*-butyl- and diphenylboronite;[9] this is also borne out by their chemical behaviour. Thus 1-ethoxycarbonylethyl di-*n*-butylboronite was readily oxidised and hydrolysed by air as in general are esters of type $RO{\cdot}BBu^n_2$,[6] whereas the corresponding vinyl compound was much more stable and the vinyl diphenylboronite (see ref. 13 for behaviour of esters $RO{\cdot}BPh_2$) did not react



(I)

perceptibly (98% recovered) with water or 3N-hydrochloric acid during five hours. It also did not co-ordinate with pyridine (see ref. 14 for ester–amine co-ordination). Similar hydrolytic stability has been observed to a smaller extent with 2-aminoethyl diphenylboronite and this has been explained as due to chelation by means of nitrogen–boron co-ordination.[15] That chelation by itself is not sufficient to account for the stability of our compounds can be realised by noting that amine complexes of boronites are still easily hydrolysed [14] and so also are the chelated [9] acyloxyboron compounds. We attribute our results as due to structures [9] (I), the aromatic character of the ring largely contributing to the stability (see also ref. 17).

Experimental

General Techniques and Preparations.—Phenylboron dichloride and diphenylboron chloride were prepared by Abel, Dandegaonker, Gerrard, and Lappert's method.[16] Refractive indices were measured on an Abbé-type refractometer. M. p.s were taken in sealed capillary tubes. The determination of the acetate radical in the presence of boron has been described above; for a typical run about 0·3 g. of sample was titrated in the presence of 100-vol. hydrogen peroxide (10 c.c.; 15 minutes' standing; Bromothymol Blue). Chlorine and the trifluoroacetate group were estimated acidimetrically (Methyl Red) as the acids formed on hydrolysis. Because of the great ease of hydrolysis of the acyloxyboron compounds, manipulations were carried out in a dry-box and for the di-*n*-butylboron carboxylates in a nitrogen-filled dry-box, to avoid oxidation. Rotatory powers are recorded for $l = 10$ cm.

Preparation of Acyloxyboron Compounds by the Elimination of Hydrogen Chloride.—These reactions were carried out on an approximately 0·05 molar scale. The exact amount of carboxylic acid in *n*-pentane (10 c.c.) was added dropwise with shaking to the appropriate chloride in *n*-pentane (10 c.c.) at 20°. Considerable heat was evolved, and hydrogen chloride was formed. All matter volatile at 20°/20 mm. was removed, to leave the acyloxyboron derivative. The results are shown in the Table.

Product	Yield † (%)	B. p./mm.	M. p. (decomp.) *	n_D^{20}	Found (%) B	AcO	$CF_3{\cdot}CO_2$	Required (%) B	AcO	$CF_3{\cdot}CO_2$
$(CF_3{\cdot}CO{\cdot}O)_3B$	100	—	88°	—	3·1	—	94·7	3·1	—	96·9
$(AcO)_2BPh$	90	—	172—174	—	5·4	56·5	—	5·3	57·3	—
$CF_3{\cdot}CO{\cdot}O{\cdot}BBu^n_2$...	98	79°/22	—	1·3800	4·6	—	47·5	4·6	—	47·5
$AcO{\cdot}BBu^n_2$	83	88—94°/16	49—52	1·4372	6·0	31·6	—	5·9	32·1	—

* Owing to disproportionation. † For liquids the yields are based on the distilled product.

Sublimation of Tristrifluoroacetyl Borate.—Sublimation of trifluoroacetyl borate (5·95 g.) at 100° at 10^{-4} mm. yielded *tetrakistrifluoroacetyl diborate* (4·00 g., 96%), m. p. 113—120°

[13] Abel, Gerrard, and Lappert, *J.*, 1957, 112, 3833.
[14] Abel, Gerrard, Lappert, and Shafferman, *J.*, 1958, 2895.
[15] Letsinger and Skoog, *J. Amer. Chem. Soc.*, 1955, 77, 2491.
[16] Abel, Dandegaonker, Gerrard, and Lappert, *J.*, 1956, 4697.
[17] Gerrard, Lappert, and Shafferman, *Chem. and Ind.*, 1958, 722.

(decomp.) (Found: B, 4·6; $CF_3{\cdot}CO_2$, 93·0. $C_6O_9F_{12}B_2$ requires B, 4·4; $CF_3{\cdot}CO_2$, 92·3%). A condensate of trifluoroacetic anhydride (1·57 g., 88%), b. p. 39° (also identified by its infrared spectrum), was trapped at −180°. The diborate and also tristrifluoroacetyl borate could not be purified by recrystallisation owing to their insolubility in solvents such as benzene, nitromethane, ether, and methylene iodide.

Preparation of Diacetyl Phenylboronate by Dephenylation.—Acetic acid (0·93 g., 2 mol.) was added dropwise with shaking to diphenylboron chloride (1·54 g., 1 mol.) at 20°. There was considerable heat of reaction and evolution of hydrogen chloride. All matter volatile at 20°/10 mm. was removed to leave diacetyl phenylboronate (1·36 g., 88%), m. p. 172° (Found: B, 5·4; OAc, 56·6%), as the sole residue. Benzene, b. p. 80° (0·60 g., 100%), identified by its infrared spectrum, was trapped at −80°.

Interaction of Trifluoroacetic Acid with Phenylboron Dichloride.—The acid (8·27 g., 2 mol.) was slowly added with shaking to the dichloride (5·75 g., 1 mol.) at 20°. Hydrogen chloride was evolved and heat of reaction noted. Benzene (1·71 g., 92%), b. p. 80° (also identified by its infrared spectrum), was removed at 20°/20 mm. and collected at −80°. Removal of all volatile matter from the *n*-pentane washings of the residue afforded unchanged phenylboron dichloride (1·57 g.) (Found: Cl, 44·3; B, 6·7. Calc. for $C_6H_5Cl_2B$: Cl, 44·6; B, 6·9%). Sublimation of the final residue at 100°/0·02 mm. yielded tetrakistrifluoroacetyl diborate (4·14 g., 76%) (Found: B, 4·3; $CF_3{\cdot}CO_2$, 91·1%).

Interaction of Acetic Acid with the n-*Butoxyboron Chlorides.*—(*a*) Acetic acid (3·22 g., 2 mol.) in *n*-pentane (10 c.c.) was added dropwise with shaking to *n*-butyl dichloroboronite (4·15 g., 1 mol.) in *n*-pentane (10 c.c.) at 20°. There was considerable heat of reaction and evolution of hydrogen chloride. Solvent and all other matter volatile at 20°/20 mm. were removed. Acetic anhydride (0·81 g., 89%) (Found: equiv., 48·0. Calc. for $C_4H_6O_3$: equiv. 51·0) was removed at 20°/0·11 mm. and collected at −80°. Removal of all matter volatile at 20°/20 mm. from the *n*-pentane washings of the residue afforded tri-*n*-butyl borate (1·31 g., 80%) (Found: B, 4·5. Calc. for $C_{12}H_{27}O_3B$: B, 4·7%), also identified by its infrared spectrum. The final residue was tetra-acetyl diborate (2·08 g., 85%), m. p. 149° (Found: B, 7·9; OAc, 85·5. Calc. for $C_8H_{12}O_9B_2$: B, 7·9; OAc, 86·3%). A trace (~5%) of *n*-butyl acetate was detected in the acetic anhydride by gas–liquid chromatography.

(*b*) This reaction was carried out as described in (*a*). Acetic acid (2·19 g., 1 mol.) and di-*n*-butyl chloroboronate (7·02 g., 1 mol.) afforded tetra-acetyl diborate (1·43 g., 86%) (Found: B, 7·7; OAc, 85·5%), tri-*n*-butyl borate (5·00 g., 89%) (Found: B, 4·6%), and acetic anhydride (0·55 g., 72%) (Found: equiv., 46·9).

Preparation of Bistrifluoroacetyl Phenylboronate and Trifluoroacetyl Diphenylboronite.—(*a*) Phenylboron dichloride (3·05 g., 1 mol.) in ether (20 c.c.) was slowly added with shaking to anhydrous sodium trifluoroacetate (5·22 g., 2 mol.) in ether (20 c.c.) at 20°. Considerable heat of reaction was noted. After shaking (2 hr.), filtration afforded a precipitate of sodium chloride (2·04 g., 91%). Removal of all matter volatile at 20°/20 mm. and subsequent washing with *n*-pentane afforded *bistrifluoroacetyl phenylboronate* (5·06 g., 84%), m. p. 104—108° (decomp.) (Found: B, 3·4; $CF_3{\cdot}CO_2$, 69·8. $C_{10}H_5O_4F_6B$ requires B, 3·5; $CF_3{\cdot}CO_2$, 72·0%].

(*b*) *Trifluoroacetyl diphenylboronite* (7·58 g., 93%), m. p. 85—93° (decomp.) (Found: B, 3·9; $CF_3{\cdot}CO_2$, 39·4. $C_{14}H_{10}O_2F_3B$ requires B, 3·9; $CF_3{\cdot}CO_2$, 40·7%), was prepared as described in (*a*), by the addition of diphenylboron chloride (5·84 g., 1 mol.) to sodium trifluoroacetate (3·97 g., 1 mol.). Attempted recrystallisation of this product and also of the one from (*a*) did not improve their purity.

Preparation of n-*Butyltrifluoroacetoxyboronous Anhydride.*—A mixture of trifluoroacetic acid (5·19 g., 4 mol.) and di-*n*-butylboronous anhydride (3·02 g., 1 mol.) was heated under reflux (6 hr.) at 90—110°. A condensate of *n*-butane (1·17 g., 89·1%) (characterised by gas–liquid chromatography by comparison with an authentic sample), b. p. −1°, was trapped at −80°. Excess of trifluoroacetic acid (2·56 g., 98·5%) (Found: equiv., 113. Calc. for $C_2HO_2F_3$: equiv., 114) was removed at 20°/0·05 mm. and collected at −80°. A crystalline residue of n-*butyltrifluoroacetoxyboronous anhydride* (3·59 g., 83·6%), after recrystallisation (benzene–chloroform), had m. p. 85—88° (Found: B, 5·7; $CF_3{\cdot}CO_2$, 58·4. $C_{12}H_{18}O_5F_6B_2$ requires B, 5·7; $CF_3{\cdot}CO_2$, 59·9%).

*Hydrolysis of Acetyl Di-*n-*butylboronite.*—Water (0·40 g., 1 mol.) in dry ether (30 c.c.) was added slowly with shaking to acetyl di-*n*-butylboronite (4·11 g., 1 mol.) at 20°. Solvent was removed at 20°/40 mm., and acetic acid (1·16 g., 88%) (Found: equiv., 58·9. Calc. for

$C_3H_4O_3$: equiv., 60·0) was subsequently removed at 20°/3 mm. and collected at −80°. Distillation of the residue afforded di-*n*-butylboronous anhydride (2·61 g., 88%), b. p. 98°/0·11 mm., n_D^{20} 1·4263 (Found: B, 8·0. Calc. for $C_{16}H_{36}OB_2$: B, 8·1%).

*Interaction of Octan-2-ol with Trifluoroacetyl Di-*n*-butylboronite.*—(+)-Octan-2-ol (2·55 g.; α_D^{20} +4·83°) in *n*-pentane (15 c.c.) was added dropwise to trifluoroacetyl di-*n*-butylboronite (4·66 g.) at 20°. Considerable heat of mixing was noted and all matter volatile at 20°/20 mm. was subsequently removed. Distillation of the residue afforded a forerun (0·81 g.) and (+)-1-methylheptyl di-*n*-butylboronite (3·98 g., 80%), b. p. 115—120°/0·4 mm., n_D^{20} 1·4275, α_D^{20} +7·84° (Found: B, 4·4. Calc. for $C_{16}H_{35}OB$: B, 4·3%). This ester had nearly the same rotatory power and sign as when prepared from the alcohol and di-*n*-butylboron chloride.[6]

Preparation of Ethoxycarbonyl-substituted Boron Esters.—(a) *2-Ethoxycarbonyl-1-methylvinyl di-*n*-butylboronite* (1·54 g., 82%), b. p. 72°/0·01 mm., n_D^{20} 1·4582 (Found: C, 65·6; H, 11·0. $C_{14}H_{27}O_3B$ requires C, 66·2; H, 10·7%), was prepared by the dropwise addition of ethyl acetoacetate (0·97 g., 1 mol.) in pentane (10 c.c.) to di-*n*-butylboron chloride (1·20 g., 1 mol.) in *n*-pentane (20 c.c.), removal of matter volatile at 20°/20 mm., and distillation.

(b) The *diphenylboronite* (3·53 g., 99%), m. p. 74—75° (Found: C, 72·5; H, 6·6. $C_{18}H_{19}O_3B$ requires C, 73·5; H, 6·5%), was prepared as in (a) from diphenylboron chloride (2·54 g., 1 mol.) and ethyl acetoacetate (1·59 g., 1 mol.).

(c) *1-Ethoxycarbonylethyl di-*n*-butylboronite* (6·70 g., 93%), b. p. 127°/21 mm. (Found: B, 4·7. $C_{13}H_{27}O_3B$ requires B, 4·5%), was prepared as in (a) from di-*n*-butylboron chloride (4·80 g., 1 mol.) and ethyl lactate (3·47 g., 1 mol.).

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THE NORTHERN POLYTECHNIC,
HOLLOWAY ROAD, LONDON, N.7.

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731. *The Infrared Spectra and Structures of Some Acyloxy-derivatives of Boron.*

By L. A. DUNCANSON, W. GERRARD. M. F. LAPPERT,
H. PYSZORA, and R. SHAFFERMAN.

The infrared spectra of a number of acyloxy-derivatives of boron are discussed. Some abnormally low carbonyl stretching frequencies are ascribed to intramolecular bonding between the carbonyl-oxygen atoms of the acyloxy-group and the boron atom to which the group is attached. The tendency for this co-ordination decreases as the electron-donor and -acceptor properties of the carbonyl group and the boron atom respectively decrease. Spectra also reveal disproportionation of certain of the acyloxy-boron compounds into carboxylic and boron acid anhydrides, apparently increasing with the capacity for co-ordination.

DURING investigations of the infrared spectra of certain acetoxy-derivatives of boron (*i.e.*, containing the grouping Me·CO·O·B⟨) some abnormally low stretching frequencies of ester-type carbonyl groups have been observed, and these have structural implications. The CO stretching frequencies of ester groups are known [1,2] to be lowered from the value of about 1740 cm.$^{-1}$ found in simple aliphatic esters by conjugation at the α-carbon atom [3]

[1] Jones and Sandorfy, " Chemical Application of Spectroscopy," Interscience Publ., Inc., New York, 1956, Chapter 4.
[2] Bellamy, " Infrared Spectra of Complex Molecules," Methuen, London, 1954, Chapter 11.
[3] Thompson and Torkington, *J.*, 1945, 640.

or hydrogen bonding,[4] and to be raised by electronegative α-substituents [5] or conjugation of the lone-pair electrons on the ether-type oxygen atom.[5]

		Carbonyl frequencies (cm.$^{-1}$) and assignments		
			Acyloxy-boron group	
Compound	State	Carboxylic anhydride	free	bonded
$Bu^n_2B{\cdot}OAc$	liquid	1825, 1757	—	1603
,,	*cyclo*hexane soln.	1709 *	—	1608
$[(AcO)_2B]_2O$	solid	—	1718	1605
$Bu^n_2B{\cdot}O{\cdot}CO{\cdot}CF_3$	liquid	—	1786	1672
$[(CF_3{\cdot}CO{\cdot}O)_2B]_2O$	solid	—	1770	1655
$PhB(OAc)_2$	solid	1815, 1745	1700	1610
$PhB(O{\cdot}CO{\cdot}CF_3)_2$	liquid	—	1761	—
$Ph_2B{\cdot}O{\cdot}CO{\cdot}CF_3$	liquid	—	1770	—
$(AcO{\cdot}BCl)_2O$	solid	1789 †	—	1587
$(CF_3{\cdot}CO{\cdot}O{\cdot}BBu^n)_2O$	solid	—	—	1689
$(CF_3{\cdot}CO{\cdot}O)_2B$	solid	—	1775, shoulder at ~1800	1661
$Bu^n_2B{\cdot}O{\cdot}CHMe{\cdot}CO_2Et$	liquid	—	1742	—
$Bu^n_2B{\cdot}O{\cdot}CMe{=}CH{\cdot}CO_2Et$	liquid	—	—	1598 ‡
$Bu^n_2B{\cdot}O{\cdot}CMe{=}CH{\cdot}CO_2Et$	CCl_4 soln.	—	—	1595 ‡
$Ph_2B{\cdot}O{\cdot}CMe{=}CH{\cdot}CO_2Et$	solid	—	—	1574 §

* Weak band due to trace of acetic acid. † Weak band due to trace of acetyl chloride. ‡ Also a strong band at 1528 cm.$^{-1}$, assigned to conjugated C=C. § Also strong band at 1531 cm.$^{-1}$ assigned to conjugated C=C.

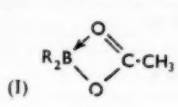
The carbonyl stretching frequencies of various acetoxy- and trifluoroacetoxy-boron compounds are listed in the Table. These compounds are mixed anhydrides of boron acids and carboxylic acids and in some cases the results show that disproportionation occurs, giving an equilibrium between the mixed anhydride and the individual carboxylic and boron acid anhydrides. However, in these cases the situation is quite clear and the carbonyl bands of the carboxylic anhydrides and the acetoxy-boron compounds can easily be differentiated and assigned. For example, in the spectrum of acetyl di-*n*-butylboronite $Bu^n_2B{\cdot}OAc$, bands at 1825 and 1757 cm.$^{-1}$ are due to some acetic anhydride present and the third band at 1603 cm.$^{-1}$ must be due to the boronite. The material is therefore more correctly formulated as the equilibrium mixture, $2Bu^n_2B{\cdot}OAc \rightleftharpoons Bu^n_2B{\cdot}O{\cdot}BBu^n_2 + Ac_2O$. The relative band intensities indicate that at room temperature much less than 50% of the boronite is disproportionated. The carbonyl stretching frequency of the mixed anhydride (1603 cm.$^{-1}$) is exceptionally low and there are only two ways in which the electron-deficient boron atom can influence this frequency so markedly. First, double-bond formation between the boron atom and the attached ether-type oxygen atom, by sharing of a lone pair from the oxygen, could complete the boron octet (*i.e.*, $\geq B\overset{\curvearrowleft}{-}O{\cdot}Ac$). This would, however, be expected to raise the carbonyl frequency, as does the similar electron displacement in vinyl or phenyl esters [5] (*i.e.*, $\overset{\curvearrowleft}{C}{=}C\overset{\curvearrowleft}{-}O{\cdot}Ac$). Secondly, the boron atom can relieve its electron-deficiency by sharing a lone pair or π-electrons from the carbonyl group (*i.e.*, $\geq B{\leftarrow}O{=}C$). Electron-withdrawal from the ester group in this manner has an obvious analogy with hydrogen-bonding of the carbonyl group and would result in a lower frequency, as observed.

This interpretation of the low carbonyl frequency is confirmed by measurements on other acetoxyboron compounds. For example, tetra-acetyl diborate $(AcO)_2{\cdot}B{\cdot}O{\cdot}B(OAc)_2$ has two carbonyl stretching bands, at 1718 and 1605 cm.$^{-1}$, of approximately equal intensities. Only two of the four acetoxy-groups can co-ordinate to the two boron atoms and these are responsible for the 1605 cm.$^{-1}$ band; the remaining two acetoxy-groups absorb fairly normally at 1718 cm.$^{-1}$.

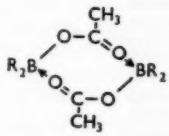
Trifluoroacetoxyboron compounds show similar effects to the acetoxyboron compounds but the carbonyl frequencies are raised 50—70 cm.$^{-1}$ by the electronegative trifluoromethyl

[4] Rasmussen and Brattain, *J. Amer. Chem. Soc.*, 1949, **71**, 1073.
[5] Hartwell, Richards, and Thompson, *J.*, 1948, 1436.

group. There is, however, less tendency for the carbonyl-oxygen of the trifluoroacetoxy-group to co-ordinate with boron than for the carbonyl-oxygen of the acetoxy-group itself, as is shown by the spectrum of $Bu^n_2B{\cdot}O{\cdot}CO{\cdot}CF_3$ which, in the liquid state, at room temperature has a band at 1786 cm.$^{-1}$ due to non-co-ordinated carbonyl groups as well as a weaker band at 1672 cm.$^{-1}$ due to co-ordinated carbonyl groups. This is consistent with competition of the electronegative trifluoromethyl group with boron for electrons from the carbonyl bond (*i.e.*, $\geq B{\leftarrow}O{=}C{\rightarrow}CF_3$). In the trifluoroacetoxy-derivatives of boron there also seems to be a smaller tendency for disproportionation to the carboxylic anhydride than in the acetoxy-derivatives.



(I)



(II)

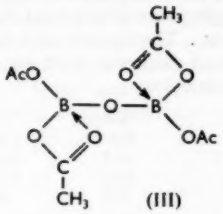
In the spectrum of liquid diacetyl phenylboronate there are, in addition to weak bands due to acetic anhydride, two carbonyl bands at 1610 (co-ordinated $\geq B{\cdot}OAc$) and at 1700 cm.$^{-1}$ (non-co-ordinated $\geq B{\cdot}OAc$). In $PhB(O{\cdot}CO{\cdot}CF_3)_2$ and $Ph_2B{\cdot}O{\cdot}CO{\cdot}CF_3$, co-ordination $C{=}O{\rightarrow}B\leq$ does not occur to a significant extent. Both these compounds have single high-frequency carbonyl bands (1761 and 1770 cm.$^{-1}$ respectively), and the only other bands in the double-bond region are relatively weak ones near 1600 cm.$^{-1}$ due to the aromatic rings. It must be concluded that electron-withdrawal by the CF_3 groups and electron-release by the phenyl groups is sufficient, in combination, to prevent chelation.

It seems clear from the above that, when conditions are suitable, the boron atoms in acetoxyboron compounds achieve a tetrahedral (sp^3) configuration by completing their octets by the formation of co-ordinate bonds with the carbonyl-oxygen atoms. This could in theory involve either intra- (*e.g.*, I) or inter-molecular (*e.g.*, II) electron-displacement. To decide between these two possibilities the spectra of dilute solutions of $Bu^n_2B{\cdot}OAc$ in *cyclo*hexane were measured. Invariably a strong band was observed at 1608 cm.$^{-1}$ together with weak bands at 1709 and near 1745 cm.$^{-1}$. The last two bands are due to a small amount of acetic acid, presumably arising from hydrolysis by traces of moisture picked up during manipulation of solvent and sample. The use of solvents which are more difficult to dry rigorously led to the production of larger amounts of acetic acid, as shown by increased absorption at 1709 cm.$^{-1}$. Over the concentration range studied (0·0244—0·0133M) the extinction of the 1608 cm.$^{-1}$ band is constant within about 5% and this small variation can be accounted for by variation in the amount of material hydrolysed. We therefore conclude that the structure of the acetyl di-*n*-butylboronite is best represented by (I). Molecular models show that the carbonyl-oxygen atom and the boron atom can approach sufficiently close for chelation. In the case of trifluoracetyl di-*n*-butylboronite the situation is not so clear because, in the liquid itself, both co-ordinated and non-co-ordinated molecules occur. By analogy with the corresponding acetoxy-compound we would expect co-ordination to be intramolecular (*i.e.*, chelation) but, because the co-ordinate bond is weaker in the trifluoroacetyl compound, rotational isomerism occurs in the liquid state to give a high proportion of molecules with non-chelated conformations. Cooling the material to −180° intensifies the low-frequency band at the expense of the high-frequency band. This could be due, however, to either an increase in dimerisation or a change in the proportion of rotational isomers.

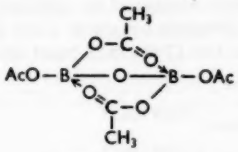
Compounds based upon the B–O–B skeleton may undergo chelation to give either four-membered (III) or six-membered (IV) rings but we have at the moment no results which distinguish between them.

Electronic effects of various groups attached to the boron atom upon its acceptor properties are shown by the following carbonyl-frequency sequences of the chelated acyloxy-groups: (*a*) $(CF_3{\cdot}CO{\cdot}O{\cdot}BBu^n)_2O$ > (*b*) $Bu^n_2B{\cdot}O{\cdot}CO{\cdot}CF_3$ > (*c*) $[(CF_3{\cdot}CO{\cdot}O)_2B]_2O$;

and (*d*) $AcO{\cdot}BBu^n_2 \approx$ (*e*) $[(AcO)_2B]_2O >$ (*f*) $(AcO{\cdot}BCl)_2O$. Thus the central oxygen atom in (*a*) can back-co-ordinate electrons to the boron atoms (B←O), thereby causing weaker co-ordination of the trifluoroacetoxy-groups in (*a*) than in (*b*). This is demonstrated by the change in carbonyl frequency from 1689 cm.$^{-1}$ for (*a*) to 1677 cm.$^{-1}$ for (*b*). The effect of the central oxygen atom in (*c*) is offset by electron-withdrawal by the second



(III)



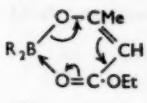
(IV)

trifluoroacetoxy-group attached to each boron atom. This brings the carbonyl frequency of the chelated trifluoroacetoxy-group in (*c*) down to 1655 cm.$^{-1}$. The carbonyl frequencies of the chelated acetoxy-groups in (*d*) and (*e*) are approximately the same, showing that a second acetyl group attached to boron in (*e*) does not offset the effect of the central oxygen atom as does the trifluoroacetoxy-group in (*c*). A further frequency lowering to 1587 cm.$^{-1}$ occurs in the spectrum of (*f*), owing to attachment of electronegative chlorine atoms to the boron atoms.

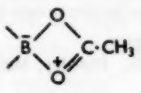
Similar effects are shown by the spectra of 1-ethoxycarbonylethyl dibutylboronite and 2-ethoxycarbonyl-1-methylvinyl dibutylboronite (*i.e.*, $Bu^n_2B{\cdot}O{\cdot}CHMe{\cdot}CO_2Et$ and $Bu^n_2B{\cdot}O{\cdot}CMe{:}CH{\cdot}CO_2Et$). The former substance has a carbonyl frequency (1742 cm.$^{-1}$) which is normal for an alkyl ester, showing that the carbonyl group is not involved in bonding to boron. On the other hand the latter has two strong bands at much lower frequencies (1598 and 1528 cm.$^{-1}$) than occur in the spectrum of enolised ethyl acetoacetate itself [4] in which chelation to a proton (*i.e.*, hydrogen-bonding) occurs. These bands, which are assigned to modes involving C=O and C=C stretching, have the same frequencies in the spectrum of a dilute carbon tetrachloride solution of the dibutylboronite and it follows that the substituted vinyloxy-group is chelated as in (V).

The diphenylboronite (V; R = Ph) has similar bands at 1574 and 1531 cm.$^{-1}$, showing that the electron release from the phenyl groups is not sufficient to restrict chelation in this case.

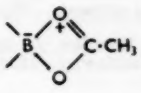
From molecular models it is clear that there is no steric hindrance to chelation in 1-ethoxycarbonylethyl dibutylboronite, and therefore its inability to chelate must be due to electronic effects. Thus the oxygen atom attached to boron in this compound must share its lone-pair electrons with the boron atom to an extent which decreases the Lewis acid strength of the boron atom below the level at which an ester-carbonyl group can co-ordinate. It appears that in oxyboron compounds co-ordination of an ester-carbonyl group is inhibited unless the lone-pair electrons of the oxygen atoms directly attached to boron are conjugate to another unsaturated system. For example, in the vinyl dibutylboronite, the electron-displacements indicated in (V) favour chelation by increasing both the electron-acceptor properties of the boron atom and the electron-donor properties of the carbonyl-oxygen atom. Similarly in acetoxyboron compounds, resonance stabilisation of the chelate ring can arise owing to contributions of structures (VIa and b) to the states of the molecules.



(V)



(VIa)



(VIb)

Experimental

Except for the compound $(AcO{\cdot}BCl)_2O$ [6] the preparation and physical constants of the boron compounds are described by Gerrard, Lappert, and Shafferman.[7]

*cyclo*Hexane, used as solvent, was dried and stored over sodium. Carbon tetrachloride was dried and distilled from phosphoric oxide. The spectra were measured with a Grubb–Parsons double-beam S3A spectrometer fitted with a sodium chloride prism, and the frequencies quoted are correct to ± 4 cm.$^{-1}$. The spectra of solid samples were determined from paraffin oil mulls and liquid samples were measured as capillary films. The spectra of solutions of $Bu^n_2B{\cdot}OAc$ in *cyclo*hexane were obtained by using a cell of fixed thickness (0·02 cm.) and the extinction data for the 1608 and the 1709 cm.$^{-1}$ band are given below.

Molar concentration	0·0244	0·0146	0·0133
Transmission (%) at 1608 cm.$^{-1}$	35	54·5	63
Optical density/concn. at 1608 cm.$^{-1}$	18·7	18·0	17·8
Transmission (%) at 1709 cm.$^{-1}$	83·2	85·7	88
Optical density/concn. at 1709 cm.$^{-1}$	3·3	4·6	4·9

Northern Polytechnic, Holloway Road, London, N.7.
Akers Research Laboratories, Imperial Chemical Industries Ltd.,
The Frythe, Welwyn, Herts.
[*Received, May 23rd*, 1958.]

[6] Gerrard and Wheelans, *J.*, 1956, 4296.
[7] Gerrard, Lappert, and Shafferman, preceding paper.

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732. *Germanium Esters. Part II.*[1] *Intermolecular Forces and Liquid Structure.*

By D. C. Bradley, L. J. Kay, J. D. Swanwick, and W. Wardlaw.

Vapour pressures and viscosities have been measured over a range of temperatures for germanium esters $Ge(OR)_4$ where R = Me, Et, Pr^n, Pr^i, Bu^n, Bu^i, Bu^s, and Bu^t. Energies and entropies of vaporisation have been calculated, together with energies and entropies of activation for viscous flow. The behaviour of germanium esters in the liquid state is discussed.

In Part I [1] were reported the densities and surface tensions of some germanium esters over a range of temperature. An analysis of their parachors suggested that germanium esters are forced, by the configuration of the alkyl group, to adopt certain preferred conformations in the liquid. For example, in the straight-chain *n*-alkyl derivatives it appears that the four $-OR$ chains are disposed in two parallel pairs inclined approximately at right angles to a common axis passing through the germanium atom; the molecule, by rotation about the long axis, can assume a roughly cylindrical shape. In the branched-chain esters this conformation is prevented by intramolecular congestion and a disc-like conformation is preferred. In an attempt to throw further light on this problem we systematically studied other physical properties of germanium esters and now report measurements of vapour pressures and viscosities over a range of temperatures.

Experimental

Germanium Esters.—These were prepared as described in Part I.[1]

Vapour Pressures.—Boiling points were measured under reduced pressure of dry nitrogen in an all-glass apparatus similar to the one used in earlier work on metal alkoxides and silicon esters.[2] Measurements for each ester were made on two different samples (*ca.* 5 c.c.), first in order of ascending pressures and then the reverse. During a "run" small fractions were distilled out at various temperatures and the boiling points rechecked. This procedure ensured that no volatile impurities were present. Pressures in the range 5—200 mm. Hg were measured

[1] Part I, Bradley, Kay, and Wardlaw, *J.*, 1956, 4916.
[2] Bradley, Mehrotra, and Wardlaw, *J.*, 1952, 5020; Bradley, Mehrotra, Swanwick, and Wardlaw, *J.*, 1953, 2025.

on a conventional mercury manometer with a travelling microscope. For each compound the results conformed to the simple equation $\log P_{mm.} = a - b/T$, and the values of a and b are given in Table 1.

Viscosities.—An all-glass viscometer of the Ostwald type was constructed with standard joints and vacuum taps to enable the sample to be distilled in directly under reduced pressure. Atmospheric moisture was rigorously excluded and measurements were made under dry nitrogen on two separate samples of each ester. The apparatus was calibrated at various temperatures between 20° and 45° with benzene and no significant variation of the apparatus constant was found. The viscometer was immersed in a thermostat (±0·1°) for at least 1 hr. at each temperature to attain thermal equilibrium. Measurements were then made in the following sequence of temperatures: 20°, 25°, 30°, 35°, 40°, 45°, 42·5°, 37·5°, 32·5°, 27·5°, and 22·5°. The esters exhibited Newtonian flow and in each case the results conformed to the simple equation $\log \eta$ (millipoises) $= c/T - d$, and the values of c and d are given in Table 1.

TABLE 1.

R in $Ge(OR)_4$	a	b	c	d	R in $Ge(OR)_4$	a	b	c	d
Me	8·28	2300	346·5	0·294	Bu^s	8·58	3260	671·0	0·929
Et	8·33	2500	463·8	0·559	Bu^i	8·79	3130	782·6	1·222
Pr^n	8·47	2870	575·7	0·787	Bu^n	8·88	3130	812·8	1·325
Pr^i	8·76	2865	567·1	0·816	Bu^t	8·41	2810	1227·8	2·368

DISCUSSION

Boiling Points and Heats and Entropies of Vaporisation.—In Table 2 are presented the boiling points under 5 mm. pressure ($T_{5·0}$) and the molar heats of vaporisation (ΔH_v, in kcal./mole). The increment in boiling point (ΔT) in ascending the homologous series of *n*-alkyl orthogermanates is also given in addition to the entropies of vaporisation at 5 mm. pressure ($\Delta S_{5·0}$, cal./deg./mole). Because it is generally accepted that a comparison of entropies of vaporisation of different compounds at the same pressure may be misleading if these compounds have appreciably different boiling points, we have adopted Hildebrand's [3,4] method of comparing entropies at the same molar concentration of vapour. Stavely and Tupman [5] have recently extended and refined Hildebrand's treatment but we have not sufficient data (*e.g.*, critical constants) to apply their method. The values for the "Hildebrand entropy" ΔS_H (cal./deg./mole) in Table 2 were calculated for a vapour concentration of 0·00507 mole/l. Some data on silicon esters [2] determined under similar conditions are also included for comparison.

TABLE 2.

R in $Ge(OR)_4$	$T_{5·0}$	ΔT	ΔH_v	ΔS_v	ΔS_H	R in $Ge(OR)_4$	$T_{5·0}$	ΔH_v	ΔS_v	ΔS_H
Me	30·0°	—	10·5	34·7	28·4	Bu^s	109·5°	14·3	37·4	30·7
Et	54·4	24·4	11·4	34·9	28·5	Bu^t	91·5	12·9	35·3	28·6
Pr^n	96·3	41·9	13·1	35·5	28·9	$Si(OEt)_4$ ...	42·1	11·2	35·5	29·3
Bu^n	140·2	43·9	14·9	36·0	29·1	$Si(OPr^i)_4$ ...	55·8	11·2	34·0	30·2
Pr^i	82·0	—	13·1	36·9	30·3	$Si(OBu^n)_4$ ...	123·4	14·8	37·4	30·6
Bu^i	113·4	—	14·2	36·7	30·0					

As a basis for comparison with the germanium esters we present in Table 3 some "Hildebrand entropies" for simpler molecules calculated from Hildebrand's [3] results.

TABLE 3.

Compound	N_2	O_2	CCl_4	$SnCl_4$	C_6H_6	Zn	Cd	Hg
ΔS_H	27·4	27·4	26·8	27·0	27·2	26·2	26·2	26·0

Apart from the metals, these compounds have $\Delta S_H \simeq 27$. Stavely and Tupman [4] consider that the diatomic molecules N_2 and O_2 are not freely rotating because they have entropies of vaporisation which are high relative to values deduced from a reference curve

[3] Hildebrand, *J. Amer. Chem. Soc.*, 1915, **37**, 970.
[4] *Idem*, *J. Chem. Phys.*, 1939, **7**, 233.
[5] Stavely and Tupman, *J.*, 1950, 3600.

of ΔS against $10^3P/T$. However, this is based mainly on mercury as a substance exhibiting unrestricted rotation and we are not convinced that mercury is an appropriate standard substance because of its metallic properties, and especially as the inert gases have higher entropies of vaporisation, and it seems improbable that mercury atoms could have freer rotation than atoms of inert gases. Accordingly we suggest $\Delta S_H = 27$ as a good value for a liquid whose molecules exhibit substantially free rotation.

It is clear that all of the substances listed in Table 2 have anomalously high ΔS_H's.

Internal Energy of Vaporisation and Molar Work of Cohesion.—Grunberg and Nissan [6] have discussed the structural implications for simple organic molecules of the energy relationships involved in vaporisation, viscous flow, and surface formation. They derived the following molar work of cohesion: $W_c = 2\gamma N^{1/3}V_l^{2/3}$, where γ is the surface tension and V_l the molar volume of the liquid. The energy per mole to overcome intermolecular attraction in the liquid is given by the internal energy of vaporisation, $E_v = \Delta H_v - P(V_g - V_l)$ where V_g is the molar volume of the vapour. The approximation $E_v = \Delta H_v - RT$ may also be used. Grunberg and Nissan [6] consider a liquid to have a statistical structure with each molecule generally surrounded by n nearest neighbours and the intermolecular forces localised in "bonds" between nearest neighbours. They suggested that in surface formation the energy required is determined by the smallest number of "bonds" which must be disrupted to expose the central molecule and that this is related to the geometrical configuration of the n nearest neighbours. In this manner they deduced that for hexagonal (close-packed), cubic (close-packed), cubic (body-centred), octahedral, and tetrahedral configurations the ratio E_v/W_c would be 4, 4, 4, 3, and 2 respectively. Hence the ratio E_v/W_c can be used to determine the configuration of molecules in the liquid. We have derived values of E_v and W_c for the germanium esters and the results are given in Table 4. These figures relate to 40° and it is assumed that the

TABLE 4.

R in $Ge(OR)_4$	E_v	W_c	E_v/W_c	$E_{visc.}/W_c$	$E_v/E_{visc.}$	R in $Ge(OR)_4$	E_v	W_c	E_v/W_c	$E_{visc.}/W_c$	$E_v/E_{visc.}$
Me	9·9	2·43	3·8	0·64	6·2	Pr^i	12·5	3·56	3·5	0·73	4·8
Et	10·8	3·30	3·3	0·64	5·1	Bu^i	13·6	4·55	3·0	0·79	3·8
Pr^n	12·5	4·00	3·1	0·66	4·8	Bu^s	13·7	4·54	3·0	0·82	3·7
Bu^n	14·3	4·66	3·1	0·66	4·6	Bu^t	12·2	4·32	2·7	1·30	2·1

latent heats quoted in Table 2 are applicable. Values of W_c were calculated from the surface tensions and densities published earlier.[1]

Viscous Flow.—Following Eyring's [7] treatment of the theory of viscous flow we have calculated activation energies ($E_{visc.}$, kcal./mole), free energies of activation ($\Delta F^\ddagger$, kcal./mole) and entropies of activation ($\Delta S^\ddagger$, cals./deg./mole) for viscous flow for the germanium esters. To illustrate the small effect of temperature on $\Delta F^\ddagger$ and $\Delta S^\ddagger$ we include in Table 5 data at 20° and 40° (except for the *tert.*-butyl ester, m. p. 23·5°).

TABLE 5.

R in $Ge(OR)_4$	Temp.	η (mP)	$E_{visc.}$	$\Delta F^\ddagger$	$\Delta S^\ddagger$	R in $Ge(OR)_4$	Temp.	η (mP)	$E_{visc.}$	$\Delta F^\ddagger$	$\Delta S^\ddagger$
Me	20°	7·73	1·58	3·29	−5·8	Pr^i	20°	13·15	2·59	4·01	$-4·8_5$
	40	6·49		3·42	−5·9		40	9·90		4·12	−4·9
Et	20	10·57	2·12	3·71	−5·4	Bu^i	20	28·10	3·58	4·56	−3·3
	40	8·36		3·83	−5·5		40	18·90		4·64	−3·4
Pr^n	20	15·10	2·63	4·07	−4·9	Bu^s	20	28·10	3·72	4·55	−2·8
	40	11·25		4·18	$-4·9_5$		40	18·60		4·62	−2·9
Bu^n	20	21·90	3·07	4·41	−4·6	Bu^t	(25)	(56·35)	5·62	(5·03)	(+2·0)
	40	15·95		4·53	−4·7		40	35·70		5·01	+2·0

Values for $E_v/E_{visc.}$ and $E_{visc.}/W_c$ are included in Table 4. We now discuss the structural implications of the data given in Tables 2, 4, and 5.

[6] Grunberg and Nissan, *Trans. Faraday Soc.*, 1949, **45**, 125.
[7] Eyring, *J. Chem. Phys.*, 1936, **4**, 283; also Glasstone, Laidler, and Eyring, "The Theory of Rate Processes," McGraw-Hill, New York, 1941.

n-*Alkyl Orthogermanates.*—The series from methyl to *n*-butyl shows the expected increase in b. p. and in the energy parameters ΔH_v, W_c, and $E_{visc.}$ with increase in size of the molecule. The values of ΔS_H increase slightly in ascending the series but this is barely significant against a probable error of *ca.* $\pm 0{\cdot}3$ unit. On the other hand, $\Delta S^{\ddagger}$ becomes steadily less negative from methyl to *n*-butyl and it is noteworthy that Moore, Gibbs, and Eyring [8] showed that in the normal alkanes from C_5 to C_{64} $\Delta S^{\ddagger}$ becomes more negative. The methyl ester appears " anomalous " in some respects. Thus ΔT from methyl to ethyl is much smaller than succeeding increments and the same applies to increments in ΔH_v, suggesting that intermolecular forces are abnormally high in the methyl ester. However, the entropy of vaporisation reveals no significant difference between the methyl ester and the higher homologues whilst for W_c and $E_{visc.}$ the increments become smaller in ascending the series. The " high " value for ΔH_v (and E_v) for the methyl ester is further reflected in the methyl ester's having abnormally large values for E_v/W_c and $E_v/E_{visc.}$ compared with the higher homologues. Grunberg and Nissan's [6] theory being applied, the high value for E_v/W_c suggests that the methyl ester has a higher " co-ordination number " in the liquid state than the other homologues. This is reasonable in view of the methyl ester's being smaller than the others and more nearly spherical in shape, and hence capable of achieving a higher symmetry in the liquid. This view is supported by the high value of $E_v/E_{visc.}$ if we apply Moore, Gibbs, and Eyring's theory.[8] They suggest that straight-chain hydrocarbons behave as quasi-crystalline liquids in which the mechanism of flow involves a co-operative movement analogous to the flow of metals by movement of dislocations in the crystal lattice and resulting in values of $E_{visc.}$ small relative to E_v. On this basis the high value of $E_v/E_{visc.}$ for methyl orthogermanate indicates a high degree of " quasi-crystallinity " in the liquid with flow by the co-operative mechanism. Increase in the length of the *n*-alkyl chain in the germanium esters lowers the symmetry (and quasi-crystallinity) and reduces the scope for flow by the co-operative mechanism.

Branched-chain Alkyl Orthogermanates.—The expected effect of chain branching on intermolecular forces and volatility is shown by the boiling points and heats of vaporisation of the isomeric butyl orthogermanates (Table 2). The ΔS_H's are all greater than 27 e.u. and it appears that even the tertiary isomer exhibits restricted molecular rotation. The energies of vaporisation (E_v) and works of cohesion (W_c) show parallel trends: $Bu^n > Bu^i \simeq Bu^s > Bu^t$, and, except for Bu^t, the ratio E_v/W_c is 3, suggesting an octahedral configuration in the liquid. The most striking feature of these results is the fact that E_{visc} shows an exactly opposite trend to E_v or W_c. This causes the ratio $E_v/E_{visc.}$ to fall rapidly in the order $Bu^n > Bu^i > Bu^s > Bu^t$ and suggests a change in mechanism of flow as the alkyl groups become more branched. In fact Moore *et al.*[8] suggested that for complex molecules having a low order of quasi-crystallinity and exhibiting restricted rotation the co-operative mechanism of flow could not operate and flow would involve molecular " jumps ". Moreover, they postulated for flow by molecular jumps that the ratio $E_v/E_{visc.}$ would be nearly 2 and $\Delta S^{\ddagger}$ positive. This is indeed the case for the *tert.*-butyl isomer and it appears that in changing from Bu^n to Bu^i to Bu^s to Bu^t the mechanism of flow changes from the co-operative phenomenon to that of individual molecular jumps. In line with this we note that $\Delta S^{\ddagger}$ becomes steadily more positive from Bu^n to Bu^t. The suggestion of less quasi-crystalline structure in the *tert.*-butyl ester is also supported by its low value for E_v/W_c. This postulated change in symmetry or quasi-crystallinity from Bu^n to Bu^t is also in accord with our suggestions for the preferred conformations of these esters based on analysis of their parachors. Thus the cylindrical molecules of the *n*-butyl ester can pack together to a certain degree but branching of the alkyl chains interferes with this packing.

BIRKBECK COLLEGE, MALET ST., LONDON, W.C.1. [*Received, April 3rd*, 1958.]

[8] Moore, Gibbs, and Eyring, *J. Phys. Chem.*, 1953, **57**, 172.

733. *The Conductivity of Some Salts in Ethanol–Water Mixtures.*

By C. W. Davies and G. O. Thomas.

The conductivities of cobaltous chloride and sulphate, magnesium sulphate, potassium bromate, silver nitrate, and zinc perchlorate in some ethanol–water mixtures at 25° c are reported and discussed.

The equivalent conductances at 25° c are reported for magnesium and cobaltous sulphates in a series of ethanol–water mixtures; some results of James [1] for zinc and copper sulphates are available for comparison. In addition measurements have been made with cobaltous chloride, potassium bromate, silver nitrate, and zinc perchlorate in 50%(w/w) ethanol.

Results

The results for 50% ethanol–water mixtures are in Table 1. To save space, the conductances of magnesium and cobaltous sulphates in other solvents are given at round concentrations in Table 2.* The results are the mean of two or more (usually four) independent runs. The solvent correction (2—4 × 10^{-7} ohm^{-1}) has been subtracted.

TABLE 1. *Conductances in 50% ethanol–water at 25°.*

	$MgSO_4$			$CoSO_4$			$CoCl_2$	
Run	10^4C	A	Run	10^4C	A	Run	10^4C	A
1	2·3375	29·01	1	1·3821	29·74	1	2·1272	43·68
2	3·2040	26·99	2	1·4680	29·65	1	2·8092	43·42
1	4·0615	25·29	2	2·2025	26·75	2	3·1009	43·28
2	4·8856	24·12	1	2·5729	25·49	1	3·9848	42·98
1	6·0615	22·62	2	3·2028	24·19	2	4·4474	42·89
2	8·3810	20·49	1	3·3806	23·61	1	6·3074	42·36
1	8·6090	20·36	2	4·4621	21·84	2	8·0239	41·97
2	11·286	18·73	1	6·5017	19·32	2	11·943	41·20
1	13·243	17·76	2	7·0107	18·97			
1	16·388	16·56	1	9·1482	17·44		$Zn(ClO_4)_2$	
2	17·258	15·97	1	12·921	15·66	Run	10^4C	A
1	24·750	14·42	3	18·698	13·54	1	2·3010	44·82
3	33·653	13·71	3	36·320	10·63	2	2·7121	44·73
4	43·581	11·80	4	44·894	9·73	2	3·7358	44·56
3	50·910	11·46	3	57·515	8·96	1	4·5556	44·35
4	70·249	10·02	4	69·132	8·44	2	5·2114	44·28
3	94·732	8·81	3	76·206	8·11	2	7·4790	43·88
			4	90·843	7·61	1	7·7885	43·79
						1	11·244	43·41
						2	14·050	42·96

	$KBrO_3$					$AgNO_3$					
Run	10^4C	A	Run	10^4C	A	Run	10^4C	A	Run	10^4C	A
1	1·5667	46·66	2	7·8058	45·75	1	2·6973	47·74	2	17·165	46·42
2	1·5838	46·62	3	10·674	45·41	2	3·1634	47·59	3	18·989	46·27
1	2·1401	46·51	4	11·030	45·31	1	3·4641	47·57	4	20·959	46·19
2	2·2936	46·47	3	12·287	45·26	2	4·0411	47·52	3	22·710	46·06
1	2·5126	46·42	4	15·424	45·02	1	4·8578	47·42	4	33·306	45·51
2	2·9334	46·31	3	23·909	44·39	2	6·4953	47·27	3	49·810	44·83
1	3·6594	46·19	4	37·904	43·71	1	8·4177	47·06	4	57·874	44·49
2	4·3081	46·13	3	50·874	43·02	1	11·938	46·77	3	86·180	43·58
1	5·8162	45·89	3	63·622	42·51				4	113·16	42·89
1	6·1361	45·80	4	78·710	41·95						

When the results for the sulphates are plotted against the square root of the concentration slopes much steeper than the limiting Onsager slope are given. This is attributed to ion-pair formation, and Owen's method [2] was used for determining Λ_0. At ethanol concentrations of 20% or more the method was unsatisfactory, and for these solutions the Λ_0 values in Table 2

* Full results are reported by G. O. Thomas, Thesis, University of Wales, 1955.

[1] James, *J.*, 1951, 153.

[2] Owen *J. Amer. Chem. Soc.*, 1939, **61**, 1393.

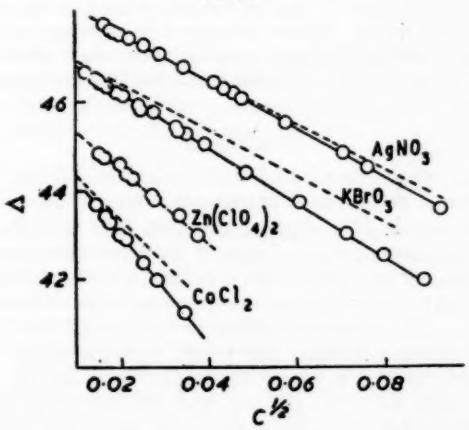
are those which, by trial and error, give the most constant K values when applied to the measurements below $C = 1 \times 10^{-3}$ (g.-equiv./l.).

TABLE 2.

	Ethanol, wt. %									
	5	10	15	20	30	40	50	10	30	50
10^4C				$MgSO_4$					$CoSO_4$	
0	112·6	95·5	81·8	71·1	55·2	48·50	43·50	95·2	57·50	42·50
1	108·4	92·0	78·2	67·2	51·2	42·48	33·20	91·2	51·7	31·50
2	106·2	89·8	76·0	65·1	49·25	39·45	30·00	88·9	48·9	27·49
3	104·3	88·1	74·4	63·6	47·75	37·42	27·53	87·0	46·75	24·49
5	101·6	85·3	71·7	61·2	45·4	34·02	24·01	84·1	43·3	21·15
7	99·4	83·2	69·7	59·2	43·45	31·70	21·72	81·8	40·95	18·89
10	96·6	80·6	67·1	56·8	40·95	29·10	19·45	78·8	38·0	16·92
20		74·6	61·5		35·3	24·26	15·22	72·1	32·45	13·17
40					29·7	19·90	12·36	64·7	27·15	10·20
70					25·0	16·77	10·00	57·9	23·25	8·36
100							8·60	53·9	21·1	7·33

Dissociation constants for comparison with the known values [3] in aqueous solution were obtained from the equation: $K = f_{\pm}^2\alpha^2C/2(1 - \alpha)$ by successive approximations. $f_{\pm}$ is the mean ion-activity coefficient and α the fraction of salt present as free ions, and it was assumed

FIG. 1.



that the limiting equations of Debye and Hückel and Onsager can be applied to the very dilute solutions studied. These assumptions cannot be separately justified, but it has been shown in previous work that in the conductivity method of determining dissociation constants the

TABLE 3.

Ethanol (wt. %)	Ethanol (mole fraction)	Density [5] (g./ml.)	Viscosity [6] (millipoise)	Dielectric constant [7]	pK $MgSO_4$	pK $CoSO_4$
0	0	0·99708	8·95	78·54	—	—
5	0·0202	0·98817	10·8	75·80	2·41 ± 0·01 (9)	—
10	0·0417	0·98043	13·2	72·80	2·47 ± 0·01 (10)	2·58 ± 0·01 (10)
15	0·0646	0·97334	16·0	69·90	2·63 ± 0·01 (7)	—
20	0·0891	0·96864	18·0	67·00	2·76 ± 0·02 (8)	—
30	0·1436	0·95067	22·0	61·10	2·97 ± 0·02 (6)	3·245 ± 0·003(9)
40	0·2069	0·93148	23·7	55·00	3·416 ± 0·005 (10)	—
50	0·2812	0·90985	23·7	49·00	3·86 ± 0·01 (7)	3·98 ± 0·01 (7)

[3] Money and Davies, *Trans. Faraday Soc.*, 1932, **28**, 609; Dunsmore and James, *J.*, 1951, 2925.
For refs. 5–7 see p. 3662.

effects of higher terms neglected in the limiting equations cancel out rather exactly; and it is believed that the K values reported are as reliable as can be obtained at the present time.[4] Table 3 gives the constants used, and the values of pK ($= -\log_{10} K$) derived from the data. The figure following the pK value gives the average deviation of the separate determinations from the mean, and the number in parentheses is the number of determinations.

The remaining salts were studied in 50% ethanol only, and the results are shown in Fig. 1. The broken lines are the limiting Onsager slopes. Of the bi-univalent salts, zinc perchlorate conforms with the theoretical slope extremely well, and clearly contains few, if any, ion-pairs at these concentrations. By direct extrapolation $\Lambda_0 = 46{\cdot}10$. Cobaltous chloride is weaker, and by Onsager's method [8] of plotting $(\Lambda + bC^{\frac{1}{2}})$ against C (where b is the Onsager slope) we obtain $\Lambda_0 = 45{\cdot}30$. It can be assumed that in the concentration range studied ion association does not go beyond the first stage: $Co^{2+} + Cl^- = CoCl^+$, and an approximate idea of the dissociation constant of the $CoCl^+$ ion may be obtained by the method previously applied to aqueous solutions.[9] For this purpose the equivalent conductances of all three ions are needed, and we have assumed (*a*) that the transport numbers at zero concentration are the same in 50% ethanol–water as in water, and (*b*) that the mobility of $CoCl^+$ is one-half that of the Co^{2+} ion. The values used are not very critical; an alteration of 30% in the mobility adopted for $CoCl^+$ alters the derived K value by only 5%. The mean pK value obtained for the $CoCl^+$ ion from eight determinations is $1{\cdot}63 \pm 0{\cdot}02$.

Of the uni-univalent salts, potassium bromate appears to be appreciably associated. Extrapolation by Onsager's method gives $\Lambda_0 = 47{\cdot}40$, and calculations of the kind applied to the bi-bivalent salts lead to a value p$K = 1{\cdot}216 \pm 0{\cdot}006$ (7 points). With this uni-univalent salt only the conductances below $C = 4 \times 10^{-4}$ could be used in the calculation; thereafter K showed a definite upward trend. Silver nitrate is a stronger salt, and direct extrapolation in conformity with the limiting Onsager equation gives $\Lambda_0 = 48{\cdot}55$. The salt probably contains ion-pairs, for the experimental line lies below the Onsager slope at all concentrations.

Discussion

Walden's rule is not obeyed in ethanol–water mixtures. If the Walden product $\Lambda_0\eta$ for magnesium sulphate is plotted against the percentage of alcohol in the solvent, the curve rises to a maximum at 15% ethanol and then falls steadily away. This is just what has been found by Bateman and Ewing [10] for strontium chloride and bromide in ethanol–water mixtures, and by Longsworth and MacInnes [11] for salts in water–methanol mixtures. It follows that if Stokes's law were used to estimate the mean ionic radius of a salt in these mixtures, the values on adding alcohol would first become smaller than that calculated for an aqueous medium and would then rise again. The same facts are shown in a different way in Fig. 2, where the fluidity ratio and the Λ_0 ratio in different solvent mixtures are compared. The fluidity ratio, ϕ(water)/ϕ(solvent), is shown by the continuous line. It is unlikely that the changes are really due to changes in the ionic radii, and it may not be without significance that the divergence first becomes serious at a solvent structure where the initial decrease in fluidity is being halted and reversed.

When the pK values of Table 3 are plotted against the reciprocal of the dielectric constant, the points are found to lie on straight lines. That of cobalt sulphate has the slope required by Bjerrum's ion-association theory; [12] that is, the mean ionic diameter of 3·78 Å derived from this theory for aqueous solutions also fits the pK results in ethanol–water mixtures. For magnesium sulphate the experimental line has a markedly steeper slope than the theoretical; the mean ionic diameters calculated from Bjerrum's equation

[4] Cf. Fuoss and Kraus, *J. Amer. Chem. Soc.*, 1957, **79**, 3310.
[5] " Internat. Critical Tables," Vol. 3, p. 116.
[6] Interpolated from " Internat. Critical Tables," Vol. 5, p. 22.
[7] Interpolated from Åkerlof, *J. Amer. Chem. Soc.*, 1932, **54**, 4132.
[8] Onsager, *Physikal. Z.*, 1927, **28**, 277.
[9] Righellato and Davies, *Trans. Faraday Soc.*, 1930, **26**, 592.
[10] Bateman and Ewing, *J. Amer. Chem. Soc.*, 1948, **70**, 2137.
[11] Longsworth and McInnes, *J. Phys. Chem.*, 1939, **43**, 239.
[12] Bjerrum, *Kgl. danske Vidensk. Selskabs*, 1926, **7**, no. 9.

XUM

for this salt fall steadily from 5·1 Å in water to 4·0 Å in 50% ethanol. James has found similar trends for zinc and copper sulphates, and has suggested that the cause may lie not in variations in effective radii, but in a divergence of the dielectric constant effective for

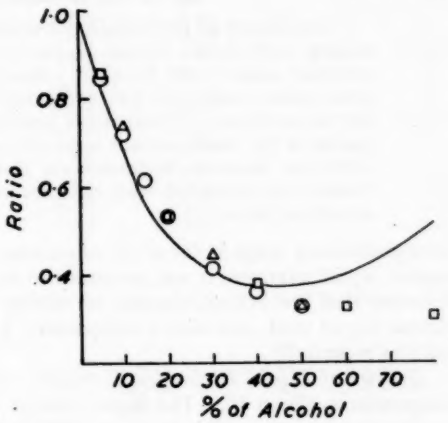


FIG. 2. *The experiment points give the plot of Λ_0 ratio, the continuous line the plot of the fluidity ratio, both against % of alcohol in the solvent.*

○ $MgSO_4$. △ $CoSO_4$. □ $SrCl_2$.

encounters from the value measured for the solvent. Another explanation of the discrepancy, which recognises the discrete nature of the solvent, is that the free energy of ion-pair formation contains a contribution from solvent-interaction energy changes in addition to that calculated from Coulomb's law.

EXPERIMENTAL

Solvent mixtures. Absolute ethyl alcohol was shaken for several hours with freshly burnt quicklime. Immediately before use it was distilled and collected under nitrogen, the first and the last portion (each 10%) being rejected. The water was prepared by mixed-bed deionisation. Solvent mixtures were made up by weight and kept under nitrogen, and the composition of each was checked by a density determination.

Salts. Zinc perchlorate was prepared by heating " AnalaR " zinc oxide with the calculated quantity of " AnalaR " perchloric acid to dissolution. The crystals obtained on cooling were washed and recrystallised from aqueous alcohol. The other salts were " AnalaR " specimens that had been recrystallised from conductivity water. Stock solutions were made up by weight, when possible, and their concentrations were checked by analysis.

Measurements. The apparatus has been described previously, and was freshly calibrated. The oil thermostat maintained a temperature of 25° ± 0·01°. The cell was of the Hartley–Barrett type with greyed electrodes, and a stream of purified nitrogen passed through it whilst additions from a weight-burette were made. The resistance readings showed no tendency to drift with time.

EDWARD DAVIES CHEMICAL LABORATORIES,
UNIVERSITY COLLEGE OF WALES, ABERYSTWYTH.

[*Received, April 17th,* 1958.]

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734. *Volume Changes on mixing Organic Liquids with Dinitrogen Tetroxide: Comparison with Sulphur Dioxide Systems.*

By C. C. Addison and B. C. Smith.

The density of pure liquid dinitrogen tetroxide, and volume changes on mixing with eleven organic liquids, have been determined over the temperature range −20° to +20°. Non-donor compounds (*e.g.*, *cyclo*hexane) give positive values of ΔV, and their mixtures approach the behaviour of regular solutions. 'Onium donor liquids (*e.g.*, acetic anhydride) give negative values of ΔV which are not symmetrical with respect to molal composition. π-Donors (aromatic hydrocarbons) give only small volume changes. The results are correlated with data for corresponding organic liquid–sulphur dioxide systems.

As a preliminary stage in the study of various physical properties of dinitrogen tetroxide–organic liquid mixtures, it was necessary to establish accurate densities for them. It was observed that the volume changes on mixing showed some correlation with the type of organic liquid used, and with corresponding liquid sulphur dioxide systems. The results are now reported.

Density of Liquid Dinitrogen Tetroxide.—Some measurements have been reported at temperatures above 0°. The liquid readily supercools below its m. p. (−11·2°) and measurements were possible down to −20° (Table 1). The values are accurate to ±0·0001,

Table 1. *Density of dinitrogen tetroxide.*

Temp.	d_4^t	Temp.	d_4^t	Temp.	d_4^t	Temp.	d_4^t	Temp.	d_4^t	Temp.	d_4^t
−20·0°	1·5364	−13·0°	1·5214	−7·0°	1·5081	0·0°	1·4927	8·0°	1·4747	17·0°	1·4538
−17·0	1·5301	−10·0	1·5147	−5·0	1·5037	3·0	1·4860	11·0	1·4677	19·0	1·4493
−15·0	1·5256	−9·0	1·5125	−3·0	1·4992	6·0	1·4793	13·0	1·4632	20·0	1·4469

and in the range above 0° agree well with more recently published values.[1-3] Three samples separately prepared gave d_4^{20} 1·44687, 1·44687, and 1·44703 (compared with 1·44750 by Bousfield [1] and 1·44703 by Pascal and Garnier [2]); two separate samples gave d_4^0 1·49268 and 1·49271, compared with 1·4925 (at 0·08°) [1] and 1·490 [2]. There is no discontinuity in the density of the supercooled liquid, and the values over the full temperature range are well represented by the equation

$$d_4^t = 1{\cdot}4927 - 2{\cdot}235 \times 10^{-3}t - 2{\cdot}75 \times 10^{-6}t^2.$$

Volume Changes on Mixing.—The molal volume V_0 of the ideal solution was obtained from the relation $V_0 = x_1V_1 + x_2V_2$, where suffixes 1 and 2 denote dinitrogen tetroxide and organic liquid respectively. The measured molal volume V of the mixture, $(x_1M_1 + x_2M_2)/d_4^t$, was plotted against mole-fraction x of the components; these units being used, the deviation ΔV $(= V - V_0)$ from the straight line joining values for pure components gives a true indication of volume changes. The variation of ΔV with composition at 20° is shown for seven liquids in Fig. 1 (for key see Table 2). The order of organic liquids so obtained agrees closely with that obtained on the basis of vapour-pressure deviations.[4] Strongest positive deviations occur with *cyclo*hexane, where molecular interaction is small. The polarity of the C–Cl bond in carbon tetrachloride results in some polar attraction, which reduces the volume expansion, and with chloroform, where there is a resultant dipole, ΔV is further reduced. The probability of molecular association between aromatic hydrocarbons and dinitrogen tetroxide by π-orbital overlap has been discussed.[5] This assists molecular orientation and association in the liquid state,

[1] Bousfield, *J.*, 1919, **115**, 45.
[2] Pascal and Garnier, *Bull. Soc. chim. France*, 1919, **25**, 309.
[3] Mittasch, Kuss, and Schlueter, *Z. anorg. Chem.*, 1927, **159**, 1.
[4] Addison and Sheldon, *J.*, 1957, 1937.
[5] *Idem*, *J.*, 1956, 1941.

TABLE 2. *Volume changes on mixing* N_2O_4 *with organic liquids.*

Key for Figs. 1 and 3	Solvent	Type	Molal volume V (ml./mole) of solvent (20°)	Maximum volume change, ΔV, on mixing with N_2O_4 20°	5°	0°	−20°
A	*cyclo*Hexane	Non-donor	108·0	+2·25	+2·0	—	—
B	Carbon tetrachloride	,,	96·5	+0·95	—	—	+0·84
C	Chloroform	,,	80·2	+0·62	—	—	+0·55
D	Benzene	π-Donor	88·9	+0·55	—	—	—
—	*p*-Xylene	,,	123·2	+0·38	—	—	—
E	Toluene	,,	106·5	+0·28	—	—	+0·20
—	Nitrobenzene	,,	102·3	−0·60	—	—	—
F	Ethyl acetate	Oxygen 'onium donor	97·8	−0·70	—	−0·60	—
G	Acetic anhydride	,,	94·5	−1·00	—	−0·84	−0·75
H	Diethyl ether	,,	103·8	−1·10	—	—	—
I	Diethylnitrosamine	Nitrogen 'onium donor	108·4	−1·35	—	—	−1·15

TABLE 3. *Temperature coefficients of density for* N_2O_4*–organic liquid mixtures.*

Composition of mixture (by wt.)	d_4^{20}	Coeff. (g. ml.$^{-1}$ deg.$^{-1}$)	Composition of mixture (by wt.)	d_4^{20}	Coeff. (g. ml.$^{-1}$ deg.$^{-1}$)
23·80% CCl_4	1·476	0·00215	33·45% EtOAc	1·215	0·00175
23·06% $CHCl_3$	1·449	0·00227	20·31% Ac_2O	1·358	0·00190
36·00% C_6H_5Me	1·160	0·00163	24·71% $Et_2N{\cdot}NO_2$	1·280	0·00170

and volume changes on mixing are small. With 'onium donor solvents, there is pronounced contraction, and in some cases maximum contraction occurs at compositions other than the 1 : 1 molar ratio. (In the solid state acetic anhydride forms a 1 : 1 compound, whereas

FIG. 1.

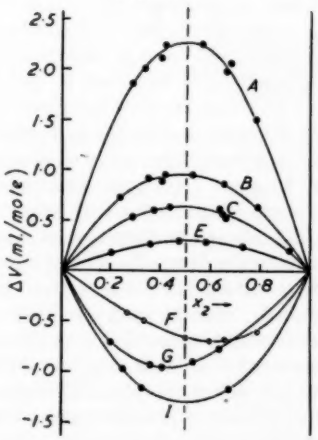
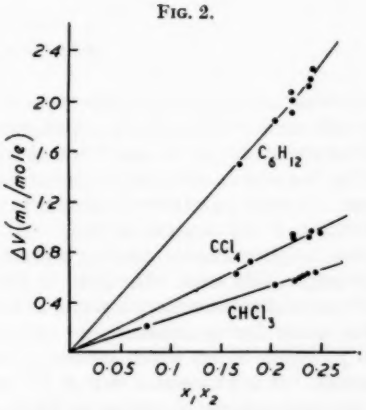


FIG. 2.



ethyl acetate and diethylnitrosamine form 2 : 1 compounds.) ΔV has been measured for eleven liquids altogether, in some cases over the temperature range −20° to +20°. Details are given in Table 2.

The extent to which mixtures with *cyclo*hexane, carbon tetrachloride, and chloroform approach regular behaviour has been tested by application of Biron's relationship $\Delta V = kx_1x_2$. Fig. 2 shows that this holds within experimental error; a wide scatter occurs if volumes rather than mole-fractions are used.

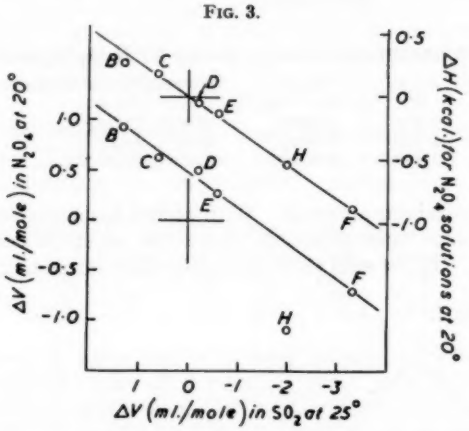
Temperature Coefficients.—The chemical reactivity of mixtures with donor solvents

differs from that of mixtures with non-donors, but is also strongly temperature-dependent. This has been attributed primarily to equilibrium (2):

$$(\text{Don})_n,N_2O_4 \overset{(1)}{\rightleftharpoons} n\text{Don} + N_2O_4 \overset{(2)}{\rightleftharpoons} (\text{Don})_n,NO^+ + NO_3^-$$

where the proportion of donor liquid (Don) present in ionic species is very small. Molecular association is clearly reflected in density changes (Fig. 1), and if equilibrium (1) varies appreciably with temperature it should be reflected in variations of the temperature coefficient of density. This has therefore been examined closely by obtaining a number of values in the range —20° to +20° for the mixtures with donors and non-donors listed in Table 3. In each case the temperature coefficient was virtually constant, the curvature of the density–temperature graph being no greater than that observed for the pure components. However, donor liquids give slightly lower coefficients, which may be significant.

FIG. 3.



Comparison with Liquid Sulphur Dioxide.—Molal volumes of mixtures of liquid sulphur dioxide with carbon tetrachloride, chloroform, benzene, toluene, and ether were calculated from densities at 25° by Lewis [6] and Adams and Rogers.[7] A single measurement by Locket [8] indicates a maximum contraction of 3·3 ml./mole for mixtures with ethyl acetate. Maximum ΔV values for these six liquids in sulphur dioxide and in dinitrogen tetroxide are plotted in Fig. 3 (for key see Table 2). A linear correlation (lower line) exists for five of the liquids, sulphur dioxide showing a greater tendency towards volume contraction than does dinitrogen tetroxide. Diethyl ether is exceptional; density measurements on the tetroxide–ether mixtures were less reproducible than in other cases, and a similar observation was made during measurement of vapour pressures. A small amount of chemical reaction probably occurs which influences some, but not all, of the physical properties of the mixture. It is of interest that if ΔV in sulphur dioxide is plotted against the heat, rather than the volume, of mixing in dinitrogen tetroxide (upper line, Fig. 3) all points lie on or near a straight line passing through the origin.

EXPERIMENTAL

Density.—This was measured by using a single-stem Pyrex-glass dilatometer fitted with a B7 ground-glass cap. The volume of the bulb was about 5 ml. The dimensions of the standard-bore capillary stem were measured by using mercury, and allowed observation of meniscus

[6] Lewis, *J. Amer. Chem. Soc.*, 1925, **47**, 626.
[7] Adams and Rogers, *ibid.*, 1939, **61**, 112.
[8] Locket, *J.*, 1932, 1501.

movement throughout the 40° cooling range. The usual corrections for vapour pressure of liquid and contraction of glass were made. Calibrated weights were corrected to vacuum, and a second identical dilatometer was used to compensate for buoyancy. For volume measurements, the dilatometer was immersed in a thermostat controlled at ±0·005°, and meniscus movements were observed with a cathetometer.

Materials.—Liquid dinitrogen tetroxide was prepared and purified as already described;[9] organic liquids were carefully purified immediately before use by accepted methods, particular care being taken to remove traces of moisture.

THE UNIVERSITY, NOTTINGHAM. [*Received, June 2nd,* 1958.]

[9] Addison, Allen, Bolton, and Lewis, *J.*, 1951, 1289.

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735. *The Synthesis of* (±)-*Ipomeamarone* [(±)-*Ngaione*] *and its Steric Isomers.*

By TAKASHI KUBOTA and TERUO MATSUURA.

(±)-Ipomeamarone has been prepared from (+)-ipomeamarone. Syntheses of (±)-*epi*ipomeamarone and (±)-ipomeamarone are described and their stereochemistry is discussed.

THE formula (I) was ascribed[1] to (+)-ipomeamarone, isolated[2] from sweet potatoes infected by *Ceratostomella fimbriata*, and its correctness was confirmed by a synthesis, previously reported in a preliminary note.[3] The details of this synthesis and related investigations on stereochemistry are reported here.

Natural (+)-ipomeamarone[4] is converted when heated with acetic anhydride–sodium acetate[5] into an inactive acetyl*iso*ipomeamarone (II) in which the tetrahydrofuran ring is opened and both asymmetric centres destroyed. Alkaline hydrolysis effects ring-closure to re-form (±)-ipomeamarone, with a complete identity of infrared spectra; the substance therefore is sterically identical with the natural compound.

The route of synthesis of (±)-ipomeamarone is shown in the annexed formulæ. The reactions proceeded in good yields as far as (III) which had the infrared spectrum to be expected (5·78 μ, saturated ester; 5·82 μ, αβ-unsaturated ester; 5·94 μ, furyl ketone; 6·07 μ, double bond). Acid hydrolysis of the ester (III), accompanied by decarboxylation, produced the keto-acid (IV), m. p. 104—105°, together with a considerable amount of resin probably owing to instability of the furan ring. The neutral portion from the hydrolysis was not unchanged ester (III), but further acid hydrolysis of it gave more of the keto-acid (IV). Esterification (diazomethane) and reduction by the Meerwein–Ponndorf reaction gave an impure product, possibly owing to some dehydration, but alkaline hydrolysis gave the acid (V; R″ = OH) in 78% yield from (IV). The methyl ester (V; R″ = OMe) has an infrared band at 5·77 μ (saturated ester), while that of the methyl ester of the acid (IV) shows a band at 5·86 μ (αβ-unsaturated ester), 5·98 μ (furyl ketone), and 6·07 μ (double bond).

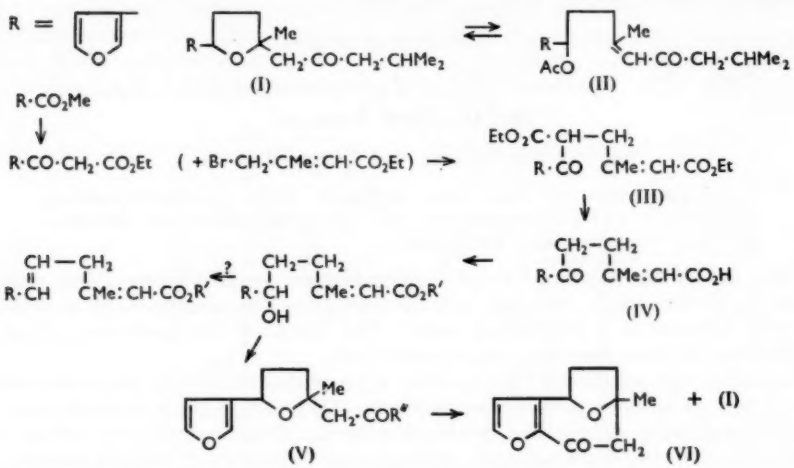
Attempts to produce the chloride (V; R″ = Cl) by the action of thionyl chloride on the acid were unsuccessful, but it was formed by treating the sodium or silver salt with oxalyl chloride.[6] The action of this chloride (V; R″ = Cl) on di*iso*butylcadmium gave two products in rather poor yields: a stereoisomer of ipomeamarone [(±)-*epi*ipomeamarone] and a crystalline compound $C_{11}H_{12}O_3$, m. p. 103—104°. The (±)-*epi*ipomeamarone was purified through its semicarbazone, m. p. 104—106°, which depressed the

[1] Kubota and Matsuura, *J. Chem. Soc. Japan*, 1953, **74**, 248.
[2] Huira, *Gifu Nosen Gakujitsu Hokoku*, 1943, No. 50.
[3] Kubota and Matsuura, *Chem. and Ind.*, 1956, 521.
[4] Kubota, Yamaguchi, Naya, and Matsuura, *J. Chem. Soc. Japan*, 1953, **74**, 44.
[5] Birch, Massy-Westropp, Wright, Kubota, Matsuura, and Sutherland, *Chem. and Ind.*, 1954, 902.
[6] Barkley, Farrar, Knowles, and Raffelson, *J. Amer. Chem. Soc.*, 1954, **76**, 5017.

m. p. (109—110·5°) of the derivative of (±)-ipomeamarone, and had a different infrared spectrum. Regeneration of the ketone gave an oil similar to ipomeamarone in b. p., n_D, and colour reactions with Ehrlich's reagent and concentrated hydrochloric acid, but differing in details of its infrared spectrum.

The assumption that it is a diastereoisomer is confirmed by conversion as above through (II) into (±)-ipomeamarone, purified through the semicarbazone (m. p. and mixed m. p. 108—110°), having the authentic infrared spectrum.

The substance ngaione, isolated [7] from *Myoporum laetum* Forst., was shown [5, 8] to have the structure (I) and was thought [5] to be a diastereoisomer of ipomeamarone on the basis



of the optical rotation of a degradation product containing only one of the two asymmetric centres. In fact, direct comparison by means of infrared spectra of the semicarbazones of (−)-ngaione and (+)-ipomeamarone shows that they are structurally identical, and therefore enantiomeric. We are informed by Professor Birch [9] that a re-investigation of the optical rotation of the degradation product of ngaione, kindly undertaken by Dr. M. D. Sutherland, confirms this conclusion and shows that the original determination was erroneous.

Investigation of the compound $C_{11}H_{12}O_3$, m. p. 103—104°, obtained above, suggests that it has the structure (VI). It formed a semicarbazone and a 2 : 4-dinitrophenylhydrazone, gave a negative Ehrlich reaction, and was stable to mineral acid. After reduction with lithium aluminium hydride the product gave a positive Ehrlich reaction and was unstable to mineral acid. This compound could have been produced only from an acid chloride (V; R″ = Cl) in which the furan ring and acid chloride side-chain are *cis* to one another.

In order to obtain further information about the stereochemistry of the uncrystallisable compounds (V; R″ = OH or Cl), the ester (V; R″ = OMe) was ozonised and then oxidised with chromic acid to give an acid fraction (A) and a neutral fraction (B). Purification of the acids (A) by distillation of the methyl esters, saponification, and crystallisation gave two dicarboxylic acids $C_8H_{12}O_5$, which must be *cis*- (m. p. 121—122°) and *trans*- (m. p. 146—147°) isomers * of (VII). Ozonolysis of the ketone (VI) gives only

* *cis* and *trans* refer to the positions of the larger groups.

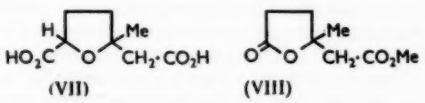
[7] McDowall, *J.*, 1925, 2200; 1927, 731; 1928, 1324.

[8] Brandt and Ross, *J.*, 1949, 2778; Birch, Massy-Westropp, and Wright, *Austral. J. Chem.*, 1953, **6**, 385.

[9] Birch, personal communication.

the acid, m. p. 121—122°, thus confirming that this is the *cis*-form. These results show that acid (V; R″ = OH) is a mixture of the *cis*- and the *trans*-isomer. We conclude that in the di*iso*butylcadmium reaction the *cis*-chloride (V; R″ = Cl) has cyclised and that the *trans*-chloride (V; R″ = Cl) has been converted into (±)-*epi*ipomeamarone, which accordingly is the *trans*-isomer: (±)-ipomeamarone should therefore be the *cis*-form. The neutral fraction (B) must be the lactonic ester (VIII), since it can be converted by Baumgarten's method [10] into the dibasic acid (IX).

The configuration of acid (V; R = OH) is presumably determined by the configuration of the double bond in its precursor (IV), but no information seems to be available on the course of such ring-closures. Ring-opening of both isomers must form a single stable isomer (II), leading on re-cyclisation to a single isomer corresponding to (±)-ipomeamarone.



(VII) (VIII) (IX) (X)

It is of considerable interest that (+)-ipomeamarone, produced by a mould, is the enantiomer of (−)-ngaione produced by a higher plant. It is also of interest that the volatile oil from black-rotted sweet potatoes contains other β-substituted furan derivatives—batatic acid [11] (X; R = CO·CH_2·CH_2·CHMe·CO_2H), ipomeanine [12] (X; R = CO·CH_2·CH_2·COMe), and β-furoic acid (X; R = CO_2H)—which are probably biological oxidation products of ipomeamarone.

Experimental

Acetylisoipomeamarone (II).—(+)-Ipomeamarone (29 g.; n_D^8 1·4870), acetic anhydride (90 c.c.), and anhydrous sodium acetate (12 g.) were refluxed for 17 hr. The dark brown solution was poured into water and extracted with ether, and the extract was washed with sodium hydrogen carbonate solution and distilled. The fraction of b. p. <146°/0·002 mm. (25 g.) was optically active ($[\alpha]_D$ +15° in ethanol) and treatment was repeated with acetic anhydride (100 c.c.) and sodium acetate (12 g.) for 27 hr. Distillation then gave a main fraction (12·9 g.), b. p. 115—118°/0·008 mm., n_D^8 1·4970, $[\alpha]_D$ 0°, $\lambda_{max.}$ 237 (ε *ca.* 7000), shoulder at 280 mμ. Crude acetyl*iso*ipomeamarone (6·6 g.) was purified by means of the Girard reagent-P, giving a ketonic fraction (3·0 g.) which on fractionation at 0·015 mm. gave: (i) b. p. <140° (0·4 g.), $n_D^{9.5}$ 1·4995, $\lambda_{max.}$ 275—278 mμ; (ii) b. p. 140—145° (1·4 g.), $n_D^{9.5}$ 1·4928, $\lambda_{max.}$ 239 mμ (ε 6850); and (iii) b. p. 145—147° (0·4 g.), $n_D^{9.5}$ 1·4890, $\lambda_{max.}$ 239 mμ (ε 7100). Fraction (iii) appears to be mainly acetyl*iso*ipomeamarone (Found: C, 68·7; H, 8·3. Calc. for $C_{17}H_{24}O_4$: C, 69·8; H, 8·3%); and the infrared spectrum is in accord: 5·77 (acetyl), 5·94 (αβ-unsaturated ketone), 6·18 μ (double bond). The material which did not react with Girard's reagent still appears to be acetyl*iso*ipomeamarone ($\lambda_{max.}$ 239 mμ).

Best results were obtained with the stored commercial substance; freshly prepared sodium acetate left about 50% of the ipomeamarone unchanged; anhydrous potassium acetate left about 25% unchanged after 37 hours' refluxing.

(±)-*Ipomeamarone.*—Fraction (iii) above (2·31 g.) was heated on the steam-bath for 1·5 hr. with 1·712N-sodium hydroxide (20·0 c.c.), and the solvent then removed under reduced pressure. The residue was diluted with water and neutralised with 1·087N-hydrochloric acid (23·6 c.c.). The product was taken up in ether and then distilled as a pale yellow oil (1·0 g.), b. p. 91—93°/0·002 mm., $n_D^{9.5}$ 1·4842, $[\alpha]_D$ 0° (Found: C, 71·7; H, 9·0. Calc. for $C_{15}H_{22}O_3$: C, 72·0; H, 8·8%). The infrared spectrum was identical with that of natural ipomeamarone. The crude semicarbazone was purified by chromatography on alumina and recrystallised from carbon tetrachloride as plates, m. p. 109—110·5° (Found: C, 62·7; H, 8·3. Calc. for

[10] Baumgarten, *J. Amer. Chem. Soc.*, 1953, **75**, 979.
[11] Kubota and Naya, *Chem. and Ind.*, 1954, 1427.
[12] Kubota and Ichikawa, *ibid.*, p. 902.

$C_{16}H_{28}O_3N$: C, 62·6; H, 8·2%). The semicarbazones of (+)-ipomeamarone and of (−)-ngaione (m. p. 132—133°) were mixed in equal quantities (2·3 mg.); the (±)-semicarbazone, m. p. 109—110·5°, was identical with the derivative above (mixed m. p., infrared spectrum).

Ethyl 3-*Furoylacetate*.—Furan-3-carboxylic acid, m. p. 121—122° (200 g.), sulphuric acid (60 c.c.), and ethanol (600 c.c.) were refluxed for 4 hr. The ester (208 g.), worked up in the usual manner, had b. p. 93—95°/35 mm. To ethyl furan-3-carboxylate (200 g.), chipped sodium metal (92 g., 4 g.-atoms) and dried ethyl acetate (550 c.c., 6·5 moles) were added in portions with stirring and heating during 6·5 hr. After being kept overnight, the mixture was diluted with benzene (200 c.c.) and refluxed with stirring for 1 hr. Further ethyl acetate (30 c.c.) was added and refluxing continued for 1 hr. in order to decompose unchanged sodium. The solution was treated with ice and hydrochloric acid and worked up in the usual manner. The ethyl 3-furoylacetate (128 g., 49·2%) had b. p. 113—116°/4 mm. after a second distillation, and n_D^{25} 1·4915 (lit., b. p. 105—107°/3 mm., n_D^6 1·4852).

Diethyl 4-3′-*Furoyl*-2-*methylbut*-1-*ene*-1 : 4-*dicarboxylate*.—To a suspension of powdered sodium (16·4 g.) in toluene (60 c.c.) and dry benzene (500 c.c.), ethyl 3-furoylacetate (130 g.) was added, and after further addition of benzene (400 c.c.) the mixture was refluxed until all sodium disappeared (6 hr.). Ethyl γ-bromo-β-methylcrotonate (148 g.) was added drop by drop to the stirred mixture, and the whole was refluxed with stirring for 9 hr. After cooling, water (500 c.c.) was added and the organic layer was separated, dried, and evaporated. Distillation of the residual oil gave the ester (III) as a pale yellow oil, b. p. 145—148°/10^{-2} mm., n_D^{24} 1·4972 (175 g., 79·6%), giving a pale brown ferric chloride colour in ethanol.

A derivative was prepared from the ester (0·4 g.), semicarbazide hydrochloride (0·3 g.), and potassium acetate (0·3 g.) in diluted ethanol by the usual method and crystallised from ethanol in colourless needles, m. p. 199—200° (Found: C, 60·95; H, 5·9; N, 9·8. Calc. for semicarbazone, $C_{17}H_{23}O_6N_3$: C, 55·9; H, 6·4; N, 11·5%).

4-3′-*Furoyl*-2-*methylbut*-1-*ene*-1-*carboxylic Acid*.—A mixture of the ester (III) (37·7 g.), acetic acid (180 c.c.), concentrated sulphuric acid (5 c.c.), quinol (1 g.), and water (30 c.c.) was refluxed for 2 hr., becoming purplish-brown. It was then evaporated under reduced pressure, diluted with water, and extracted with ether. The ethereal solution was extracted with sodium hydrogen carbonate solution, washed with water, dried, and evaporated. Distillation of the residual oil gave a neutral compound, b. p. 136—139°/10^{-2} mm., n_D^{19} 1·5180, $\nu_{max.}$ 5·89, 5·98, and 6·06 μ.

The *semicarbazone* of this compound was prepared in the usual manner and crystallised from ethanol in colourless plates, m. p. 144—145° (Found: C, 57·4; H, 6·6; N, 14·1). $C_{14}H_{19}O_3N_3$ requires C, 57·3; H, 6·5; N, 14·3%). The neutral compound (10 g.) was hydrolysed by the procedure described above. A neutral part (4·3 g.; recovered material) and an acidic part (3·4 g.) were obtained. Recrystallisations of the acidic part from carbon tetrachloride gave the acid, 103—104°, described below.

Acidification of the above sodium hydrogen carbonate solution with diluted hydrochloric acid gave a dark brown oil which solidified. The solid was filtered off, dried (crude acid, 12·0 g.), and extracted with hot carbon tetrachloride. Evaporation of the solvent left crude crystals of 4-3′-*furoyl*-2-*methylbut*-1-*ene*-1-*carboxylic acid*, m. p. 90—95° (8·6 g.). Repeated recrystallisation from carbon tetrachloride furnished the pure acid as colourless plates, m. p. 103—104° (Found: C, 63·5; H, 5·9. $C_{11}H_{12}O_4$ requires C, 63·5; H, 5·8%).

Excess of ethereal diazomethane was added to the above acid in ether and the solution left overnight. The methyl ester distilled at 102—103°/10^{-2} mm. as a colourless oil, n_D^7 1·5160, $\lambda_{max.}$ 5·86 (αβ-unsaturated ester), 5·98 (furyl ketone), and 6·07 μ (double bond).

5-3′-*Furyltetrahydro*-2-*methyl*-2-*furylacetic Acid* (V; R″ = OH).—The preceding ester (40 g.) was reduced under Meerwein–Ponndorf conditions with aluminium *iso*propoxide (prepared from 13·2 g. of aluminium and 150 c.c. of propan-2-ol) in propan-2-ol (100 c.c.). The crude hydroxy-ester, worked up in the usual manner, was obtained as a yellow oil. It was refluxed with sodium hydroxide (10·8 g.) in ethanol (200 c.c.) and water (150 c.c.) for 1 hr., then evaporated *in vacuo* and acidified with hydrochloric acid, and the separated oil was extracted with ether. The ethereal layer was washed with water, then dried and evaporated. The residue (39·0 g.) was fractionated *in vacuo*. After sublimation of a small amount of the recovered keto-acid, the acid distilled at 121—123°/10^{-2} mm. as a yellow viscous oil, n_D^{19} 1·4990 (29·5 g., 78%). The acid was methylated with diazomethane in the usual method. The methyl ester had b. p. 87—89°/10^{-2} mm., n_D^{17} 1·4820, $\lambda_{max.}$ 5·77 μ (saturated ester).

5-3′-*Furyltetrahydro-2-methyl-2-furylacetyl Chloride* (V; R″ = Cl).—(*a*) The above acid (n_D^{19} 1·4990; 16·1 g.) in ethanol (40 c.c.) was neutralised with 1·67N-methanolic sodium methoxide (44·4 c.c.). The initial pale yellow colour of the solution became yellowish-brown when excess of alkali was added (equiv., 212. Calc. for $C_{11}H_{14}O_4$: equiv., 210). The solvent was evaporated *in vacuo*, and benzene (50 c.c.) was added to the residue and distilled off. Repeating this procedure once more gave the sodium salt of the acid as a syrup. Freshly distilled oxalyl chloride (14·1 g.) in dry benzene (30 c.c.) was added to the sodium salt in benzene (60 c.c.), containing a few drops of pyridine, drop by drop with ice-cooling during 10 min. After being kept at room temperature for 1·5 hr., the mixture was warmed at 50° for 30 min. Separated sodium chloride was filtered off rapidly and washed with dry benzene. The combined filtrates were evaporated to dryness *in vacuo* at room temperature. The acid chloride (V; R = Cl) thus obtained was immediately used in the next reaction.

(*b*) The acid (2·0 g.) in ethanol (5 c.c.) was neutralised with 1·005N-sodium hydroxide (10·02 c.c.), and 10% aqueous silver nitrate solution was added. The white precipitate of silver salt was filtered off, washed with water and dried over phosphoric oxide at 80° *in vacuo* for 1 hr., forming a brown powder (2·92 g.). Oxalyl chloride (1·3 g.) in dry benzene (15 c.c.) was added to a gelatinous solution of the silver salt in dry benzene (30 c.c.), and the mixture was warmed at 60° for 30 min. and at 80° for 30 min., until the gas evolution ceased. The benzene was evaporated under reduced pressure, dry benzene (20 c.c.) was added, and the solid was filtered off rapidly. The filtrate was used immediately in the next reaction.

trans-5-3′-*Furyltetrahydro-2-methyl-2-2′-oxoisohexylfuran* [(±)-epi*Ipomeamarone*] *and the* $C_{11}H_{18}O_3$ *Ketone* (VI).—To a solution of *iso*butylmagnesium bromide, prepared from magnesium (4·6 g.), *iso*butyl bromide (26 g.), and ether (100 c.c.), powdered anhydrous cadmium chloride (17·4 g.) was added in portions with stirring and ice-cooling. The mixture gave a negative Gilman–Schulz reaction after refluxing for 10 min. Ether was distilled off, dry benzene (120 c.c.) was added, and then benzene (20 c.c.) was distilled off to remove the remaining ether. To the solution of di*iso*butylcadmium thus obtained, the acid chloride (V; R″ = Cl) prepared according to the method (*a*) (16·1 g.) was added in dry benzene (50 c.c.), rapidly with vigorous stirring at room temperature. The mixture was refluxed with stirring for 20 min., decomposed with ice-water, and acidified with diluted hydrochloric acid. The benzene layer was separated and evaporated. The residue was dissolved in ether, and the ethereal solution was washed with aqueous sodium hydrogen carbonate solution, dried, and evaporated. Distillation of the residual oil (12·2 g.) gave a pale yellow oil (7·6 g.), b. p. 105—145°/10^{-2} mm., which solidified. The solid was washed with light petroleum and dried (2·4 g., 16%). Recrystallisation from carbon tetrachloride gave the pure *ketone* as colourless needles, m. p. 103—104° (Found: C, 68·8; H, 6·6. $C_{11}H_{18}O_3$ requires C, 68·7; H, 6·3%), giving a pale yellow colour with tetranitromethane and a negative Ehrlich's reaction.

The 2 : 4-*dinitrophenylhydrazone* of this ketone crystallised from ethanol–ethyl acetate in reddish-orange needles, m. p. 223—224° (Found: N, 14·6. $C_{17}H_{18}O_6N_4$ requires N, 15·1%). The *semicarbazone*, recrystallised from ethanol, had m. p. 239° (Found: C, 57·7; H, 6·2; N, 16·4. $C_{12}H_{21}O_3N_3$ requires C, 57·8; H, 6·1; N, 16·9%).

The filtrate and the washing of the $C_{11}H_{18}O_3$ ketone were combined and evaporated. The residual oil was distilled *in vacuo*, giving crude (±)-*epi*ipomeamarone (2·5 g., 13%), b. p. 99—103°/10^{-2} mm., n_D^{21} 1·4910; it had a bitter taste and the same pleasant odour as ipomeamarone, but its refractive index and infrared spectrum showed that it was impure.

From the crude *epi*ipomeamarone (1·5 g.), semicarbazide hydrochloride (1·0 g.), and potassium acetate (1·0 g.), the *semicarbazone* was obtained as a sticky mass; it was passed in benzene (60 c.c.) through alumina (45 g.) and recrystallised from carbon tetrachloride and light petroleum in plates, m. p. 104—106° (Found: C, 62·8; H, 8·4; N, 13·6. $C_{16}H_{25}O_3N_3$ requires C, 62·5; H, 8·2; N, 13·7%). The mixed m. p. with the semicarbazone of (±)-ipomeamarone was 97—100°, and the infrared spectra did not coincide.

(±)-*epi*Ipomeamarone semicarbazone (267 mg.), oxalic acid (0·25 g.), water (1·5 c.c.), and ethanol (3 c.c.) were heated on water-bath for 2 hr., then evaporated *in vacuo*, and the residue was neutralised with aqueous sodium hydrogen carbonate. The separated oil was extracted with ether, dried, and recovered. Distillation gave (±)-epi*ipomeamarone* (0·10 g.), b. p. 92—95°/10^{-2} mm., n_D^{19} 1·4812 (Found: C, 70·95; H, 8·8. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·9%). It became pale yellow when kept for several days, like ipomeamarone, had a strongly bitter taste, and gave a purple-red colour with the Ehrlich reagent and an orange-red one with

concentrated hydrochloric acid. Its infrared absorption is very similar to that of natural ipomeamarone, but not identical.

Epimerisation of (±)-epi*Ipomeamarone to* (±)-*Ipomeamarone*.—Crude (±)-*epi*ipomeamarone (n_D^{11} 1·4910; 2·2 g.), potassium acetate (0·9 g.), and acetic anhydride (7·0 c.c.) were refluxed for 17 hr. The dark brown solution was poured into water and extracted with ether. The ethereal solution was washed with water, dried, and evaporated. Distillation of the residue gave fractions: (i) b. p. >111°/10^{-2} mm., $n_D^{11\cdot5}$ 1·4930 (0·2 g.); (ii) b. p. 111—115°/10^{-2} mm., $n_D^{11\cdot5}$ 1·4984 (0·85 g.); (iii) b. p. <115°/10^{-2} mm., $n_D^{11\cdot5}$ 1·5020 (0·8 g.). The main fraction (ii) had $\lambda_{max.}$ 5·77 (acetyl) and 6·18 μ (double bond).

Fraction (ii) (0·8 g.) in ethanol (20 c.c.) was heated with aqueous N-sodium hydroxide (5 c.c.) on the water-bath for 1 hr. The mixture was evaporated *in vacuo*, diluted with water, and extracted with ether. The ethereal solution was evaporated, and the residual oil was fractionated *in vacuo*. The main fraction was obtained as a yellow oil, b. p. 100—104°/10^{-2} mm., n_D^{11} 1·4965 (0·41 g.). This oil, semicarbazide hydrochloride (0·3 g.), and potassium acetate (0·3 g.) were dissolved in dilute ethanol and kept for 3 days. The semicarbazone was obtained as a sticky mass, which was chromatographed in benzene (20 c.c.) on alumina (20 g.), then recrystallised from carbon tetrachloride and light petroleum, in plates, m. p. 108—110° (Found: C, 62·6; H, 8·3; N, 14·3. Calc. for $C_{16}H_{25}O_3N_3$: C, 62·5; H, 8·2; N, 13·7%). The m. p. of this compound was undepressed on admixture with the semicarbazone, m. p. 109—110·5°, of (±)-ipomeamarone, which was prepared from natural ipomeamarone, and the infrared absorption curves were identical.

Reduction of the $C_{11}H_{12}O_3$ *Ketone by Lithium Aluminium Hydride*.—The $C_{11}H_{12}O_3$ ketone (0·7 g.) was refluxed with lithium aluminium hydride (0·1 g.) in absolute ether (55 c.c.) with stirring for 30 min. Excess of the reagent was decomposed with ethyl acetate; the product isolated by the usual method was pale brown and did not crystallise. It gave a deep orange colour with tetranitromethane. Addition of concentrated hydrochloric acid to its ethanolic solution showed a greenish-brown colour in the upper layer and a pink colour in the lower layer. Addition of *p*-dimethylaminobenzaldehyde and concentrated hydrochloric acid to the ethanolic solution showed a greenish-brown colour in the upper layer and a purple red in the lower layer (Ehrlich reaction).

Ozonisation of the Ester (V; R″ = OMe).—The ester (7·6 g.) in chloroform (20 c.c.) was treated with ozonised oxygen (4%) for 7 hr. The solvent was removed under reduced pressure, and the residual ozonide was decomposed with a mixture prepared from potassium dichromate (7·8 g.), concentrated sulphuric acid (10·5 g.), and water (50 c.c.). Next morning, the mixture was extracted with ether for 10 hr. The ethereal solution was extracted with sodium hydrogen carbonate solution, and then evaporated to give a yellow oil (2·8 g.) as the neutral part. The hydrogen carbonate solution was acidified and extracted with ether for 15 hr., and the ethereal solution was evaporated. The acidic part was divided into a volatile part (formic acid) and a non-volatile part by vacuum-evaporation at room temperature. Distillation of the above neutral part (2·8 g.) gave a lactonic ester (VIII) (1·2 g.), b. p. 120—125°/3—4 mm., n_D^5 1·4608, $\lambda_{max.}$ 5·66 (five-membered lactone) and 5·77 μ (ester). This lactonic ester (1·1 g.) was refluxed in benzene (3 c.c.) with thionyl chloride (3 g.) for 3 hr. (cf. ref. 10) then treated with ethanolic hydrogen chloride (10 c.c., saturated at 0°) with ice-cooling for 20 min. and evaporated under reduced pressure. The residue was heated at 200°/15 mm. and the resulting unsaturated diester distilled at 98—100°/2 mm. (0·9 g.). This compound was heated with N-sodium hydroxide (20 c.c.) and ethanol (10 c.c.) on the water-bath for 2 hr., and the solution was evaporated and acidified with hydrochloric acid. Recrystallisations of the resulting precipitate from ethyl acetate, gave the *trans*-α-dihydro-β-methylmuconic acid (IX) as plates, m. p. 160—161°. Baumgarten reported that the *cis*-acid had m. p. 118—120° but the m. p. of the above compound coincides with that (m. p. 158—160°) of the *trans*-acid.

cis- *and* trans-5-*Carboxytetrahydro*-2-*methyl*-2-*furylacetic Acid* (VII).—The above non-volatile acidic part was methylated with diazomethane in ether. The dimethyl ester (2·0 g.) distilled at 103—105°/0·01 mm. and had n_D^5 1·4555. It (951 mg.) was heated in ethanol (2 c.c.) with 0·971N-sodium hydroxide (12 c.c.) on the water-bath for 25 min., and the hydrolysate was neutralised with 1·027N-sulphuric acid (2·23 c.c.) (equiv., 102. Calc. for $C_{10}H_{16}O_5$: equiv., 108). The solution was acidified with dilute sulphuric acid (Congo-red) and extracted continuously with ether for 10 hr. Evaporation of ether left a yellow syrup from which crystals separated at 0°. After treatment with a small volume of ethyl acetate, the crystals were

collected. The trans-*acid* (VII) crystallised from ethyl acetate in plates, m. p. **146—147°** (*ca.* 300 mg.) (Found: C, 51·2; H, 6·6%; equiv., 95. $C_8H_{12}O_5$ requires C, 51·1; H, 6·4%; equiv., 95), $\lambda_{max.}$ 5·75 and 6·00 μ (in Nujol) 5·78 μ (in dioxan). Methylation of the *trans*-acid with diazomethane gave the dimethyl ester, b. p. 90—110° (bath)/2 mm., $n_D^{6·5}$ 1·4551, $\lambda_{max.}$ 5·77 μ (ester).

Ozonisation of the $C_{11}H_{12}O_3$ *Ketone.*—The ketone (0·6 g.) in chloroform (20 c.c.) was ozonised with ice-cooling for 2 hr. The solvent was distilled *in vacuo*, and the residual ozonide was decomposed with ice-cooling and stirring with potassium dichromate (1·2 g.), concentrated sulphuric acid (1·6 g.), and water (10 c.c.). After being stirred for 2 hr. and kept overnight, the mixture was extracted with ether for 10 hr. The ethereal solution was dried and evaporated. The residual yellow syrup (0·51 g.) deposited crystals when seeded with the above *cis*-acid. After treatment with a small volume of ethyl acetate, the crystals were filtered off and recrystallised twice from ethyl acetate. The m. p. (119—121°) of the colourless crystals was undepressed on admixture with the *cis*-acid (m. p. **121—122°**).

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INSTITUTE OF POLYTECHNICS, OSAKA CITY UNIVERSITY,
MINAMIOGIMACHI 12, KITAKU, OSAKA, JAPAN. [*Received, June 24th,* 1957.]

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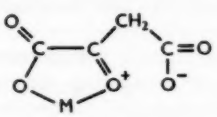
736. *The Interaction of Transition-metal Ions with Oxaloacetic Acid. Part I. The Rôle of Chelate Compounds in the Decarboxylation.*

By E. GELLES and R. W. HAY.

The nature of the chelate compounds formed by transition-metal ions with oxaloacetic acid in aqueous solution has been investigated spectrophotometrically and potentiometrically. The mechanism of the catalysed decarboxylation is discussed.

A VARIETY of reactions in solution are catalysed by metal ions. The presence of metal–substrate complexes or chelate compounds has been demonstrated in many cases, but catalytic power and complex stability have been related quantitatively in only a few instances. The primary rôle of the metal ion in chelate compounds undergoing chemical change is to attract electrons. Withdrawal of electrons from the reaction centre in the substrate may facilitate reaction; however, the catalytic effect of the metal ion is governed not only by the degree of interaction with the substrate in the initial state of reaction, but also by the interaction in the transition state. Metal-ion catalysis of some oxidations



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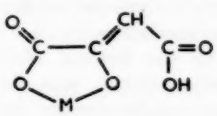

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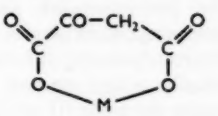

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involves electron transfer from the ligand;[1] withdrawal of electrons from the reaction centre in the substrate is exemplified by the catalysed hydrolysis of certain organic esters,[2] the halogenation of oxo-esters,[3] and the decarboxylation of β-oxo-carboxylic acids.[4]

One such reaction is the metal-ion catalysed decomposition of oxaloacetic acid into pyruvic acid and carbon dioxide. This reaction is of some biological importance.

Krampitz and Werkman [5] and Krebs [6] showed that decarboxylation was accelerated

[1] Taube, *J. Amer. Chem. Soc.*, 1947, **69**, 1418; 1948, **70**, 1216; Duke, *ibid.*, 1947, **69**, 2885.
[2] Kroll, *ibid.*, 1952, **74**, 2034; Hoppé and Prue, *J.*, 1957, 1775.
[3] Pedersen, *Acta Chem. Scand.*, 1948, **2**, 252, 385.
[4] *Idem, ibid.*, 1949, **3**, 676; 1952, **6**, 243, 285; Prue, *J.*, 1952, 2331; Gelles and Clayton, *Trans. Faraday Soc.*, 1956, **52**, 353.
[5] Krampitz and Werkman, *Biochem. J.*, 1941, **35**, 595.
[6] Krebs, *ibid.*, 1942, **36**, 303.

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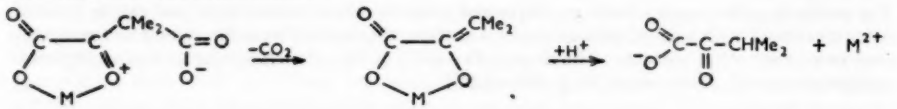
by various bi- and ter-valent cations. Kornberg, Ochoa, and Mehler [7] observed the appearance and decline of a strong absorption band at 260—300 mμ when metal ions were added to oxaloacetic acid under certain conditions. They attributed this to the slow formation of a strongly absorbing enolic complex B, which disappeared on decarboxylation.

Steinberger and Westheimer [8] showed that decarboxylation of αα-dimethylethoxaloacetic acid was not catalysed by metal ions, indicating that the catalytically active species formed by αα-dimethyloxaloacetic acid was a five-membered ring α-oxo-carboxylate chelate compound. They obtained chemical and spectroscopic evidence for a mechanism involving an enolic intermediate:



Dimethyloxaloacetic acid cannot form an enolic complex of type B, and so by analogy a ketonic complex A seemed likely to be the catalytically active species in the decarboxylation of oxaloacetic acid. Pedersen [9] interpreted the kinetics of the copper- and zinc-ion catalysed decomposition of oxaloacetic acid at low pH and metal-ion concentration in terms of the first-order decomposition of the acid, its two anions, and a species MA, where M^{2+} is the metal ion and A^{2-} the oxaloacetate anion. Williams [10] suggested that in addition to α-oxo-carboxylate complexes a dicarboxylate complex C might also be formed, and that this could retard decarboxylation under certain conditions.

Inadequate explanations have been advanced for the observed retardation of the reaction at high pH and metal-ion concentration.[10,11] Previous work has established that at low pH and low concentration of metal ion the catalytically active species must be the complex A, but it has produced no clear evidence (i) on whether a catalytically inactive complex B is also formed, (ii) if this is formed slowly enough to account for the spectrophotometric observations,[7,12] (iii) whether these observations in fact provide evidence for a strongly absorbing enolic pyruvate intermediate, (iv) on what the thermodynamic stabilities of the ketonic and enolic complexes, A and B, are, (v) how the proportion of these two complexes changes with pH, and whether increasing concentrations of the enolic complex at a high pH might account for the observed retardation in the rate of decarboxylation, (vi) whether other complexes, such as the dicarboxylate complex C, are also present under some conditions, and (vii) whether there is any correlation between the thermodynamic stability of the complexes and the catalytic power of the metal ions.

Our potentiometric and spectrophotometric studies indicate the rôle a number of chelate compounds play in the decarboxylation.

Thermodynamic information on the ketonic chelate compounds, which are the kinetically active species in decarboxylation, was obtained by comparing association constants for acids (I) and (II). Spectrophotometric studies demonstrated the presence of enolic chelate compounds which are not decarboxylated. Spectrophotometric studies on the chelate compounds of oxaloacetic acid (I) and its ethyl ester (III) have shown that oxaloacetate chelate compounds are formed very rapidly. The rise of optical density to a maximum, observed with some metal oxaloacetates under certain conditions, is due to formation of a strongly absorbing enolic pyruvate intermediate, which subsequently ketonises.

The measurement of association constants and rates of decarboxylation for metal oxaloacetates is described in detail in the following papers. In Part II, comparison of the

[7] Kornberg, Ochoa, and Mehler, *J. Biol. Chem.*, 1948, **174**, 159; Speck, *ibid.*, 1949, **178**, 315.
[8] Steinberger and Westheimer, *J. Amer. Chem. Soc.*, 1951, **73**, 429.
[9] Pedersen, *Acta Chem. Scand.*, 1952, **6**, 243, 285.
[10] Williams, *Nature*, 1953, **171**, 304.
[11] *Idem*, *Biol. Rev.*, 1953, **28**, 381.
[12] Nossal, *Austral. J. Exp. Biol.*, 1949, **27**, 143, 313.

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association constants for oxaloacetates with those for oxalates and succinates indicates the relative stabilities of keto-carboxylate and dicarboxylate chelate compounds of different ring size, and also shows that interaction of metal ion and substrate in the transition state of decarboxylation is likely to be much stronger than interaction in the initial state. In Part III the rate coefficients for catalysis by transition-metal ions are examined, and catalysis is related to the degree of interaction of metal ion and substrate in the transition state of decarboxylation.

Results

The metal-ion catalysed decomposition of oxaloacetic acid to pyruvic acid and carbon dioxide involves the interaction of metal ions with oxaloacetate in the initial state, and with pyruvate in the final state. These states can be studied directly by thermodynamic methods, while interaction in the transition state is indicated by kinetic measurements.

For the initial state, experiments were made with oxaloacetic acid (I), αα-dimethyloxaloacetic acid (II), which cannot enolise, ethyl oxaloacetate (III), which cannot be decarboxylated or form a dicarboxylate complex, and ethyl αα-dimethyloxaloacetate (IV), which cannot enolise or be decarboxylated and can only form a ketonic α-oxo-carboxylate complex.

$HO_2C{\cdot}CO{\cdot}CH_2{\cdot}CO_2H$ (I) $HO_2C{\cdot}CO{\cdot}CMe_2{\cdot}CO_2H$ (II) $HO_2C{\cdot}CO{\cdot}CH_2{\cdot}CO_2Et$ (III) $HO_2C{\cdot}CO{\cdot}CMe_2{\cdot}CO_2Et$ (IV)

Association constants at 25°.

Oxaloacetic Acid (I).—A detailed study of the association equilibria is described in the following paper. In the pH range investigated the significant association equilibria are

$$M^{2+} + A^{2-} \rightleftharpoons MA;\ K_{MA} = \{MA\}/\{M^{2+}\}\{A^{2-}\} \quad . \quad . \quad . \quad . \quad . \quad (1)$$

and

$$M^{2+} + MA \rightleftharpoons M_2A^{2+};\ K_{M_2A^{2+}} = \{M_2A^{2+}\}/\{M^{2+}\}\{MA\} \quad . \quad . \quad . \quad (2)$$

where M^{2+} represents a metal ion, A^{2-} the oxaloacetate anion, and K_{MA} and $K_{M_2A^{2+}}$ are the thermodynamic association constants (Table 1).

Table 1. *Association constants of oxaloacetates.*

	Ca^{2+}	Mn^{2+}	Co^{2+}	Zn^{2+}	Ni^{2+}	Cu^{2+}
$10^{-2}K_{MA}$	0·4	0·7	1·4	1·7	3·2	75
$10^{-2}K_{M_2A^{2+}}$	<1	<1	2	2	1·5	—

αα-Dimethyloxaloacetic Acid (II).—The ionisation constants were calculated from the pH of mixtures of the acid with varying proportions of alkali.[13] The pH values were extrapolated to the time of addition of alkali (following paper).

If the total concentrations of the dicarboxylic acid and of sodium hydroxide are a and b respectively, and

$L = b + [H^+]$, $M = a - b - [H^+]$, $N = 2a - b - [H^+]$, $[OH^-] \ll [H^+]$, then

$$[\{H^+\}^2 L f_2/N] = [\{H^+\} M f_2/N f_1]K_1 + K_1K_2 \quad . \quad (3)$$

or

$$X = YK_1 + K_1K_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where K_1 and K_2 are the two thermodynamic ionisation constants. Square brackets and braces are used to indicate concentrations and activities, respectively. f_1 and f_2 are ionic activity coefficients for univalent and bivalent ions, calculated from Davies's equation

$$-\log f_z = 0{\cdot}5z^2\left(\frac{I^{\frac{1}{2}}}{1 + I^{\frac{1}{2}}} - 0{\cdot}2I\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

The ionic strength I is calculated by successive approximations. K_1 and K_2 are obtained from the slope and intercept of the linear plot of X against Y. The results of some pH measurements and the quantities X and Y are given in Table 2.

[13] Speakman, *J.*, 1940, 855.

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The values obtained for the ionisation constants can be compared with approximate values of 3×10^{-2} and $1{\cdot}7 \times 10^{-5}$ obtained [8] by an indicator method at $I = 0{\cdot}5$, and corrected to zero ionic strength.

In the presence of copper the pH changed with time because of decarboxylation of the copper

TABLE 2. *Ionisation constants of αα-dimethyloxaloacetic acid.*

10^3a	5·76	5·67	5·76	5·59	5·52
10^3b	2·88	3·41	4·56	6·74	9·40
pH	2·66	2·77	$3{\cdot}31_5$	$4{\cdot}02_5$	4·99
10^3X	298	185	136	0·98	0·062
10^6Y	142	93·8	40·8	−20·7	−28·4

$K_1 = 1{\cdot}7 \times 10^{-2}$; $K_2 = 2{\cdot}4 \times 10^{-5}$

chelate compound; measurements could be made only over a limited range of pH and metal-ion concentration. The pH curve was extrapolated to the time of addition of metal ion. The two ionisation equilibria of the acid (II) are

$$H_2A \rightleftharpoons HA^- + H^+ \quad \text{and} \quad HA^- \rightleftharpoons A^{2-} + H^+ \quad . \quad . \quad . \quad . \quad (6)$$

If the only significant association equilibrium is

$$M^{2+} + A^{2-} \rightleftharpoons MA; \quad K_{MA} = \{MA\}/\{M^{2+}\}\{A^{2-}\} \quad . \quad . \quad . \quad . \quad (7)$$

we have for the total concentration of acid (II)

$$c_a = [H_2A] + [HA^-] + [A^{2-}] + [MA] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

for the total copper-ion concentration

$$c_m = [M^{2+}] + [MA] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

and for electroneutrality ($[OH^-] \ll [H^+]$)

$$2[M^{2+}] + [Na^+] + [H^+] = [Cl^-] + [HA^-] + 2[A^{2-}] \quad . \quad . \quad . \quad . \quad (10)$$

The ionic strength and the ionic activity coefficients are obtained by successive approximations:

$$I = \tfrac{1}{2}\left(4[M^{2+}] + [H^+] + [HA^-] + 4[A^{2-}] + [Na^+] + [Cl^-]\right) \quad . \quad . \quad . \quad (11)$$

From eqns. (6)—(10) we obtain

$$[H_2A]\left(2 + K_1/\{H^+\}f_1\right) = [Cl^-] + 2c_a - 2c_m - [Na^+] - [H^+] \quad . \quad . \quad . \quad (12)$$

The concentrations of all other species, and hence the association constant K_{MA}, can be calculated.

TABLE 3. *Association constant of copper αα-dimethyloxaloacetate.*

10^3c_a	10^3c_m	10^3[HCl]	pH	I	$10^{-3}K_{MA}$
5·61	1·96	5·10	2·07	0·0141	55
5·38	3·85	7·40	1·99	0·0215	51
5·54	3·85	2·53	$2{\cdot}16_5$	0·0169	45
5·26	7·41	7·12	2·00	0·0316	40

In view of errors due to rapid decarboxylation of the chelate compound the constancy of the values of K_{MA} given in Table 3 must be regarded as satisfactory, although the range of pH studied is too small to exclude the presence of other complexes. It is noted that the average value of K_{MA}, 48×10^3, is of the same order of magnitude as the association constant of copper oxaloacetate (cf. Table 1).

Ethyl Oxaloacetate (III).—The thermodynamic ionisation constant of this monobasic acid was determined in the usual way, by measurements with a glass electrode, to be $1{\cdot}8 \times 10^{-3}$, which is slightly smaller than the first ionisation constant of oxaloacetic acid ($2{\cdot}79 \times 10^{-3}$).

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Measurements of pH on the copper chelate compound could not be interpreted in terms of the association equilibria:

$$M^{2+} + A^- \rightleftharpoons MA^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

$$M^{2+} + 2A^- \rightleftharpoons MA_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

The data in Table 4 show that the hydrogen-ion concentration can exceed the initial ester concentration when cupric chloride is added. This implies that in addition to equilibria (13) and (14) there is appreciable formation of an enolic complex with the displacement of a proton,

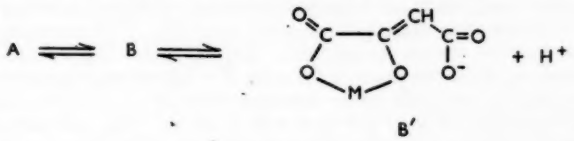
$$M^{2+} + A^- \rightleftharpoons MA_e + H^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

In contrast to ethyl oxaloacetate, oxaloacetic acid can form an enolic complex B from which a further proton will only be displaced at a higher pH.

TABLE 4. *Formation of an enolic copper complex from ethyl oxaloacetate.*

10^3[III]	2·00	1·96	1·92	1·88	1·85	1·82	1·78
10^3[$CuCl_2$]	—	1·96	3·85	5·66	7·40	9·09	10·71
pH	$2·90_5$	2·84	$2·80_5$	$2·78_5$	2·77	$2·75_5$	$2·74_5$

Eqn. (1) represents the formation of A and B. Potentiometric measurements on oxaloacetates were made in a pH range in which the enolic complex B′ is not significant.



B′

Pyruvic Acid.—A value of $3·24 \times 10^{-3}$ had been obtained [9] for the thermodynamic ionisation constant. If the monobasic acid is represented by HA

$$HA \rightleftharpoons A^- + H^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (16)$$

and if the only significant association equilibrium is

$$M^{2+} + A^- \rightleftharpoons MA^+; \qquad K_{MA^+} = \{MA^+\}/\{M^{2+}\}\{A^-\} \quad . \quad . \quad . \quad . \quad (17)$$

we have for the total concentration of metal

$$c_m = [M^{2+}] + [MA^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (18)$$

for the total concentration of acid

$$c_a = [HA] + [A^-] + [MA^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (19)$$

and for electroneutrality

$$[H^+] + 2[M^{2+}] + [Na^+] + [MA^+] = [Cl^-] + [A^-] \quad . \quad . \quad . \quad . \quad . \quad (20)$$

If, on the other hand, the only significant association equilibrium is

$$M^{2+} + 2A^- \rightleftharpoons MA_2; \qquad K_{MA_2} = \{MA_2\}/\{M^{2+}\}\{A^-\}^2 \quad . \quad . \quad . \quad . \quad (21)$$

then eqns. (18)—(20) become

$$c_m = [M^{2+}] + [MA_2] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (22)$$

$$c_a = [HA] + [A^-] + 2[MA_2] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (23)$$

$$[H^+] + 2[M^{2+}] + [Na^+] = [Cl^-] + [A^-] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (24)$$

In either case

$$[HA] = [Cl^-] + c_a - 2c_m - [Na^+] - [H^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (25)$$

the ionic strength and activity coefficients are obtained as before, and the concentrations of all other species can be calculated.

The results of some pH measurements on copper pyruvate are given in Table 5. Association

constants were calculated on the assumption of there being only one complex, MA^+ or MA_2. It can be seen that the association constant for MA_2 remains approximately constant, while that for MA^+ changes as the pyruvate : copper ratio is increased; the predominant species is clearly MA_2.

TABLE 5. *Association constant of copper pyruvate.*

10^3c_a	10^3c_m	$10^4[Cl^-]$	$10^4[Na^+]$	pH	$\log_{10} K_{MA^+}$	$\log_{10} K_{MA_2}$
2·33	5·0	105	5·9	2·83	2·3	5·0
2·33	5·0	105	11·9	2·98	2·2	4·9
2·39	5·0	105	17·8	3·17	2·3	4·9
7·13	10·0	21	2·96	2·75	3·1	4·8
9·50	10·0	21	3·95	2·69	4·2	4·8

The monobasic acids, ethyl oxaloacetate and pyruvic acid, tend to form chelate compounds of the type MA_2 with no net charge. The compounds of ethyl oxaloacetate are more stable than those of pyruvic acid, which appear to be entirely ketonic. The dibasic acids oxaloacetic acid and αα-dimethyloxaloacetic acid tend to form chelate compounds of the type MA with no net charge, and these appear to have association constants of the same order of magnitude.

Chelate compounds from oxaloacetate.

The Ketonic Chelate Compound A.—Chelate compounds of oxaloacetic acid are not entirely ketonic. The ketonic compounds are decarboxylated to a strongly absorbing enolic pyruvate intermediate, as are those of αα-dimethyloxaloacetic acid (II). The monoester (IV), however, forms only stable ketonic chelate compounds. Fig. 1 shows the variation of extinction coefficient with wavelength for the anion of the ester (IV) and for its copper chelate compound. Experiments were carried out with anion concentrations of 1×10^{-3} and $3{\cdot}37 \times 10^{-3}$M and with copper concentrations of 1×10^{-2} and $3{\cdot}33 \times 10^{-2}$M. The association constants for the copper chelate compounds of esters (III) and (IV) are of the same order of magnitude. With the above concentrations the anion of ester (IV) should be completely chelated, and this is borne out by the constancy of the extinction coefficient as the copper concentration is increased. The α-oxo-acid peak occurs at 338 mμ ($\varepsilon = 43$). At 295 mμ, which is $\lambda_{max.}$ for the enolic chelate compounds, ε is 27 for the anion of ester (IV), and 68 for the copper chelate compound. Ketonic chelate compounds of α-oxo-carboxylates with other transition-metal ions are also expected to have extinction coefficients of around 70 at 295 mμ. This is borne out by further spectrophotometric measurements described below.

The Enolic Chelate Compound B.—Enols HO·CR:CH·CO·R′ have absorption maxima at about 260 mμ; on chelation with transition-metal ions the maximum absorption of the enolate ion is shifted to higher wavelength, and the extinction coefficient is increased two- or three-fold. Studies of enolic chelate compounds in chloroform show that $\lambda_{max.}$ and ε are not greatly affected by the nature of the bivalent ion.[14]

Fig. 2 shows that the peak at *ca.* 260 mμ is due to the enol of oxaloacetic acid. Fig. 3 shows the variation of extinction coefficient with wavelength for oxaloacetates (I) and (III) in ether and light petroleum (b. p. 40°). Both oxaloacetic acid and ethyl oxaloacetate appear to be completely enolised ($\lambda_{max.} = 260$ mμ, $\varepsilon = 8800$). (Oxaloacetic acid is not decarboxylated in these solvents.) Fig. 4 relates to the copper enolate of ethyl ethoxaloacetate, $Cu[EtO_2C(CO^-):CH\cdot CO_2Et]_2$ (in chloroform; $\lambda_{max.} = 295$ mμ, $\varepsilon = 2 \times 10^4$). The enolic peak of the oxaloacetate (III) at 260 mμ and the shift of $\lambda_{max.}$ to 295 mμ on chelation of the oxaloacetate with Cu^{2+}, Ni^{2+}, Zn^{2+}, and Co^{2+} ions in aqueous solution is illustrated in Fig. 5. Enolic oxaloacetate complexes are expected to have $\lambda_{max.} = 295$ mμ ($\varepsilon \sim 2 \times 10^4$), a value independent of solvent or the nature of the transition-metal ion.

Speed of Formation of Chelates.—Addition of metal ions to oxaloacetic acid under certain conditions produces a rise of optical density with time, which has been attributed [7,12] to the slow formation of the enolic complex B. The speed of formation of the chelate compounds of ethyl oxaloacetate (III), which cannot be decarboxylated, has now been measured under comparable conditions and shown to be very fast. The optical density first measured 45 sec. after addition of metal ion changed very little with time (Table 7). The formation of a strongly absorbing intermediate on decarboxylation must therefore clearly play a part in determining

[14] Belford, Martell, and Calvin, *J. Inorg. Nuclear Chem.*, 1956, **2**, 11.

the changes in absorption spectra of metal oxaloacetates. The copper compounds are formed at a measurable rate at a high pH, but for the other metal ions chelation appears to be complete within a fraction of a minute at pH <6.

Keto–Enol Equilibria.—Previous studies [15] of the enol content of oxaloacetic acid in aqueous

FIG. 1. *Variation of* ε *with* λ *for* (1) $^-O_2C{\cdot}CO{\cdot}CMe_2{\cdot}CO_2Et$, (2) *the copper chelate of compound* $HO_2C{\cdot}CO{\cdot}CMe_2{\cdot}CO_2Et$.

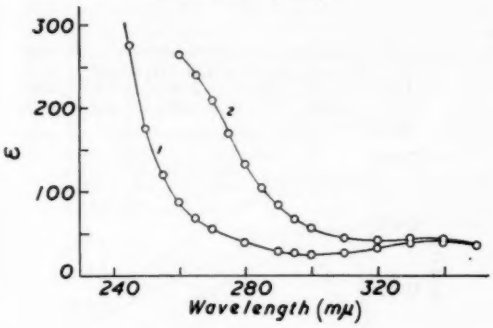
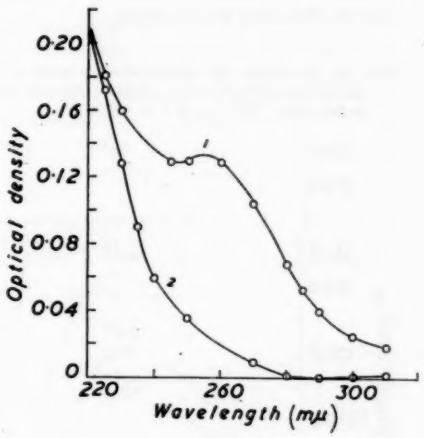


FIG. 2. *Variation of optical density with* λ *for* (1) $HO_2C{\cdot}CO{\cdot}CH_2{\cdot}CO_2H$, (2) $HO_2C{\cdot}CO{\cdot}CMe_2{\cdot}CO_2H$ (*both* $1{\cdot}25 \times 10^{-4}$M).



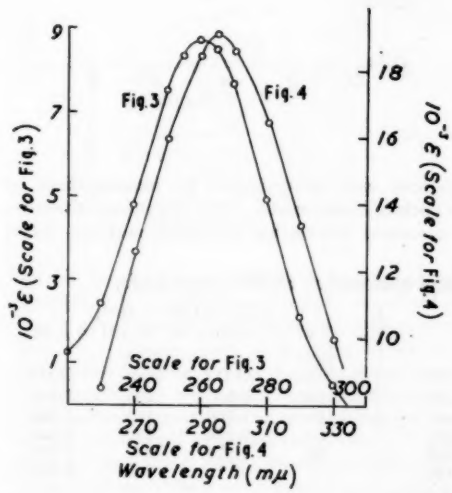


FIG. 3. *Variation of* ε *with* λ *for* $HO_2C{\cdot}CO{\cdot}CH_2{\cdot}CO_2H$ *in ether and in light petroleum* (*b. p.* 40°) *and for* $HO_2C{\cdot}CO{\cdot}CH_2{\cdot}CO_2Et$ *in ether.*

FIG. 4. *Variation of* ε *with* λ *for* $Cu[EtO_2C{\cdot}CO{\cdot}\dot{C}H{\cdot}CO_2Et]_2$ *in chloroform.*

solution have been conflicting. By use of a value of 8800 for $\varepsilon_{max.}$ of the enol, Nossal's spectrophotometric data [12] can be interpreted in terms of about 3% of enol at pH 2 increasing to 9% at pH 5·5. At this pH the acid is almost entirely in the form of the dianion. The enol content, as indicated by the optical density at 260 mμ, remains constant as the pH is increased, until an enolate ion is formed with the loss of a third proton at a much higher pH.

The enol content of oxaloacetic acid and its anions has been studied by comparing the

[15] Meyer, *Ber.*, 1912, **45**, 2860; Hantzsch, *Ber.*, 1915, **48**, 1407.

extinction coefficients at 260 mμ of acids (I) and (II) at different values of pH. The values ε (I) = 420, ε (II) = 22, and ε (enol) = 8800 indicate an enol [$HO_2C{\cdot}C(OH){:}CH{\cdot}CO_2H$] content of 4—5% in undissociated oxaloacetic acid (in perchloric acid). At pH 6, ε (I) = 850, ε (II) = 92, and ε (enol) = 8800 indicate 9% of enol [$^-O_2C{\cdot}C(OH){:}CH{\cdot}CO_2^-$] for the dianion of oxaloacetic acid. In the above pH range optical densities changed with time owing to decarboxylation, and values were extrapolated to zero time. At pH 13 complete enolisation to the trianion $^-O_2C{\cdot}CO^-{:}CH{\cdot}CO_2^-$ is indicated by the stability of the solution. No evolution of carbon dioxide or change in optical density with time was detected with acid (I), in contrast to acid (II) which continues to decompose at this pH. The extinction coefficient of the enolate ion (ε_{260} = 3200) is lower than that for the enols.

FIG. 5. *Variation of optical density with λ for* $NaO_2C{\cdot}CO{\cdot}CH_2{\cdot}CO_2Et$ ($1{\cdot}25 \times 10^{-4}$M) *with metal ions* ([$M^{2+}$] = $3{\cdot}3 \times 10^{-4}$M).

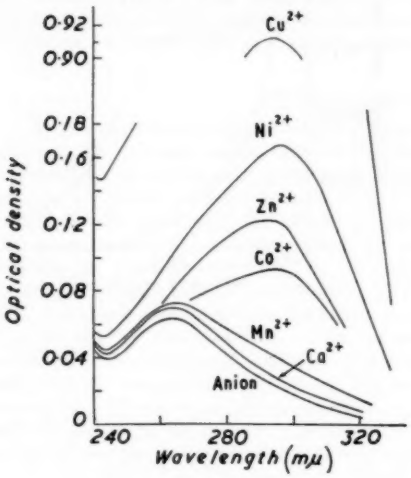
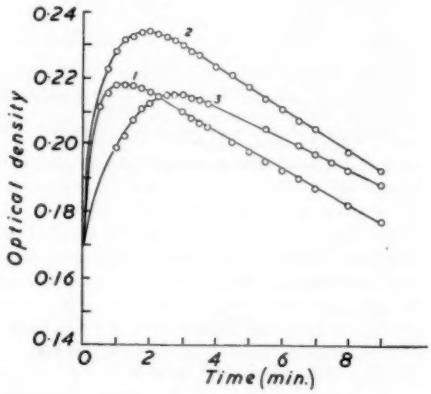


FIG. 6. *Variation of optical density with time* (λ = 290 mμ) *for* $HO_2C{\cdot}CO{\cdot}CH_2{\cdot}CO_2H$. [I] = $1{\cdot}25 \times 10^{-4}$M, [$Zn^{2+}$] = $3{\cdot}36 \times 10^{-4}$M, [Acetate] = 0·01M, (1) pH = 5·30, (2) pH = 5·66, (3) pH = 5·94.



Keto–enol equilibria in the metal oxaloacetates were investigated by measurement of optical densities at 295 mμ ($\lambda_{max.}$ for the enolic chelate compounds). The total concentration of chelate compound was calculated from the measured association constants and the initial

TABLE 7. *Speed of formation of ethyl oxaloacetate chelate compounds.*

[III] = $1{\cdot}14 \times 10^{-4}$, [$Zn^{2+}$] = $3{\cdot}20 \times 10^{-4}$M						[III] = $1{\cdot}20 \times 10^{-4}$, [$Cu^{2+}$] = $3{\cdot}23 \times 10^{-4}$M, pH = 5·34			
pH	time (sec.)	O.D.[a]	pH	time (sec.)	O.D.[a]	time (sec.)	O.D.[a]	time (sec.)	O.D.[a]
5·0	45	0·0725[b]	6·5	60	0·463	45	1·10	120	1·323
5·5	45	0·122[b]	,,	90	0·474	60	1·160	150	1·342
6·0	45	0·207[b]	,,	120	0·477	75	1·236	180	1·349
6·5	45	0·457	,,	480	0·480	90	1·274	240	1·350
			,,	600	0·480			300	1·350

[a] At 295 mμ. [b] Steady value.

concentrations, and the approximate proportions of ketonic and enolic forms, A and B, were estimated by using the values ε_{295} (A) = 70 and ε_{295} (B) = 20,000.

The proportion of enolic complex increases with pH for ethyl oxaloacetate (III), since the formation of the enolic complex must involve the displacement of a proton (eqn. 15). The variation with pH is illustrated in Table 8. Under the conditions of these experiments the monoester is almost completely chelated. At low pH and sufficiently high concentration of

zinc ion the optical density corresponds to a concentration of ketonic chelate compound ($\varepsilon = 70$) equal to the initial concentration of ester (III).

TABLE 8. *Keto–enol equilibria for zinc and copper ethyl oxaloacetates.*

10^4[III]	1·25	1·10	10^4[III]	1·25	1·25	1·25	1·25
10^4[Zn^{2+}]	333	3·04	10^4[Cu^{2+}]	333	333	6·73	3·33
pH	2·75	6·50	pH	2·24	2·54	4·34	5·34
O.D. at 295 mμ	0·009	0·48	O.D. at 295 mμ	0·20	0·51	1·13	1·36
Enolic complex (%)	0	22	Enolic complex (%)	8	20	45	55

With oxaloacetic acid the position of the keto–enol equilibrium between A and B is independent of pH. The loss of a proton from the enol B to give the complex B′ should occur at high pH, but the enol content of the metal oxaloacetates does not appear to increase below pH 6 or 6·5. With the known association constants and extinction coefficients Nossal's spectrophotometric data [12] on copper oxaloacetate can be interpreted. In the pH range 4—6 the optical densities extrapolated to zero time indicate a constant proportion (*ca.* 40%) of enolic complex. Experiments on copper oxaloacetate ([I] = $1·25 \times 10^{-4}$, [Cu^{2+}] = 10^{-1}M) at pH 2 and 3 gave extrapolated values of optical density between 0·9 and 1·0. The optical density falls very rapidly with time owing to decarboxylation. These values show that the same proportion of enolic copper complex is maintained over the pH range 2—6.

FIG. 7. *Variation of optical density with time* ($\lambda = 295$ mμ) *for* $HO_2C{\cdot}CO{\cdot}CH_2{\cdot}CO_2H$. [I] = $1·25 \times 10^{-4}$M, [M^{2+}] = $3·3 \times 10^{-4}$M, pH = 6·35.

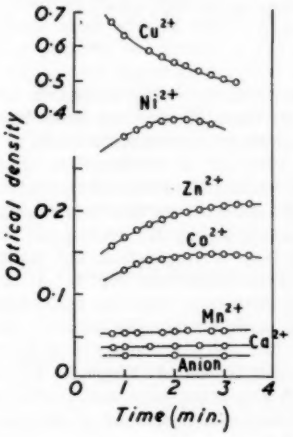
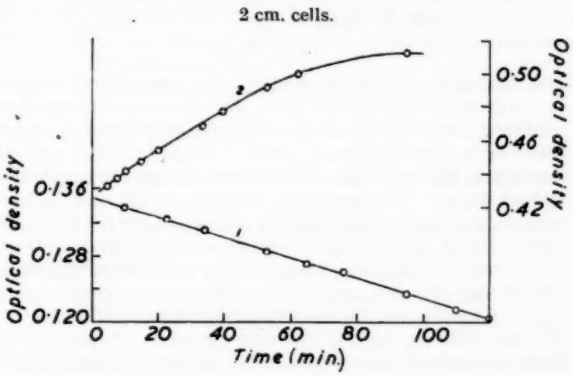


FIG. 8. *Variation of optical density with time* ($\lambda = 260$ mμ) *for* $HO_2C{\cdot}CO{\cdot}CH_2{\cdot}CO_2H$. (1) [I] = $1·25 \times 10^{-4}$M, pH = 2·0 (left ordinate), (2) [I] = $5·05 \times 10^{-4}$M, pH = 6·1 (right ordinate).



Experiments with high concentrations of zinc ion at pH 2—3 indicate 15—20% of enol. This content appears to be maintained up to pH 6·5. Fig. 6 shows the optical density–time curves for several experiments in the pH range 5—6·5; the rise is due to the formation of a strongly absorbing enolic pyruvate intermediate. The initial optical density is independent of pH and with the known association constant and extinction coefficient gives a proportion of enolic zinc complex of about 15%.

Fig. 7 shows the optical density–time curves for a typical set of experiments with the series of transition-metal ions; the rise is again attributed to formation of an enolic pyruvate intermediate on decarboxylation. The results of these experiments are collected in Table 9. Optical densities are values extrapolated to 30 sec. after addition of metal ion. Owing to uncertainties in the extrapolation of optical densities, in the association constants, and in the various extinction coefficients, the proportions of enolic complex given are approximate.

TABLE 9. *Keto–enol equilibria for metal oxaloacetates.*

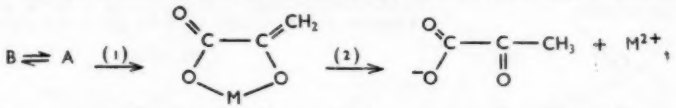
Oxaloacetate dianion: initial pH = 6·35.
$[I] = 1{\cdot}25 \times 10^{-4}$M, $[M^{2+}] = 3{\cdot}33 \times 10^{-4}$M.

	Dianion	Ca^{2+}	Mn^{2+}	Co^{2+}	Zn^{2+}	Ni^{2+}	Cu^{2+}
10^4[MA]	—	0·14	0·24	0·37	0·43	0·58	1·25
O.D. at 295 mμ	0·025	0·035	0·050	0·12	0·15	0·27	1
O.D. (B)	—	0·013	0·03	0·10	0·13	0·25	1
Enolic complex (%) ...	—	5	6	13	15	22	40

Pyruvate chelate compounds

The spectra of freshly prepared aqueous solutions of pyruvic acid and of metal pyruvates show no evidence of enolic species. Pyruvic acid and its anion give α-keto-acid peaks at 325 mμ ($\varepsilon = 5$) and 318 mμ ($\varepsilon = 22$). Copper pyruvate shows no absorption maximum and appears to be almost entirely ketonic ($\varepsilon_{295} \sim 200$).

A comparison of the optical density–time curves for the metal chelate compounds of ethyl oxaloacetate, which is not decarboxylated (Table 7), and for the metal oxaloacetates (Figs. 6 and 7) shows that the rise in optical density with time for the oxaloacetates (other than the copper complex) must be due to formation of a strongly absorbing species on decarboxylation. This is believed to be an enolic pyruvate intermediate, which subsequently ketonises:



The variation of optical density with wavelength suggests that the enolic pyruvate has an absorption maximum at a somewhat lower wavelength than B, and an extinction coefficient of several thousand. The disappearance of A and B on decarboxylation leads to a decrease in optical density, and a maximum will only be observed if ketonisation (2) is sufficiently slow to allow build-up of intermediate. It is found that the time of maximum optical density decreases with decrease of pH, and at low pH there is no maximum. The behaviour at two values of pH is illustrated for the unchelated acid in Fig. 8. At low pH the rate of fall of optical density (corrected for pyruvic acid) with time corresponds to the manometric rate of decarboxylation. Data for zinc oxaloacetate are illustrated in Fig. 6. If the rate of step (2) were simply proportional to hydrogen-ion concentration, then the maximum optical densities and the corresponding times should vary in an easily predictable manner with pH and with the ratio of the rate constants of steps (1) and (2). Measurements have been made in buffered and in unbuffered solutions of zinc oxaloacetate in the pH range 5—6·5 at 270 and 290 mμ. These measurements indicate that step (2) is a composite one, probably involving displacement of the metal ion by a proton and the catalysed ketonisation of the enol.

EXPERIMENTAL

Chemicals.—Oxaloacetic acid (Light & Co.) had m. p. 152° (decomp.) (Found, by titration against alkali: *M*, 132·6. Calc. for $C_4H_4O_5$: *M*, 132·1). Ethyl ethoxaloacetate was prepared by condensation of diethyl oxalate and ethyl acetate with sodium ethoxide.[16]

Ethyl oxaloacetate was prepared by alkaline hydrolysis of the copper enolate of ethyl ethoxaloacetate at room temperature.[17] Recrystallised from benzene it had m. p. 98° [Found: C, 44·8; H, 5·1%; *M* (by titration against alkali), 161·6. Calc. for $C_6H_8O_5$: C, 45·0; H, 5·0%; *M*, 160·1].

tert.-*Butyl αα-dimethylethoxaloacetate.* This was prepared by condensing diethyl oxalate and *tert.*-butyl *iso*butyrate with sodiotriphenylmethane.[8, 18, 19] Since the reaction times are critical, and have not been adequately reported, details are given: *tert.*-Butyl *iso*butyrate (0·19 mole) was added with shaking to sodiotriphenylmethane (0·19 mole) in ether (1300 ml.). After 25 min. at room temperature diethyl oxalate (0·19 mole) was added with shaking. After another 15 min. glacial acetic acid (15 ml.) was added and the mixture was extracted with

[16] Rossi and Schinz, *Helv. Chim. Acta*, 1948, **31**, 473.
[17] Wislicenus and Endres, *Annalen*, 1902, **321**, 381.
[18] *Org. Synth.*, Coll. Vol. III, p. 142.
[19] Hudson and Hauser, *J. Amer. Chem. Soc.*, 1941, **63**, 3156.

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water. The ether solution was washed with saturated sodium hydrogen carbonate solution and dried, the solvent distilled off, and the residue fractionated. *tert.*-Butyl αα-dimethylethoxaloacetate (23 g.; 46%) had b. p. 104—105°/4 mm., n_D^{20} 1·4252 (Found: C, 58·8; H, 7·9. Calc. for $C_{10}H_{20}O_5$: C, 59·0; H, 8·2%).

αα-Dimethyloxaloacetic acid was prepared by hydrolysis of the ester. The removal of the *tert.*-butyl group by hydrogen bromide in acetic acid and of the ethyl group by concentrated hydrochloric acid has been described.[8] The overall yield was 35%. The acid had m. p. 105° (decomp.) (from benzene) [Found: C, 44·8; H, 4·8%; *M* (by titration against alkali), 161·4. Calc. for $C_6H_8O_5$: C, 45·0; H, 5·0%; *M*, 160·1].

Ethyl αα-dimethylethoxaloacetate (yield 61%), b. p. 122—123°/15 mm., was prepared by condensing diethyl oxalate and ethyl *iso*butyrate with sodiotriphenylmethane [19] (Found: C, 55·8; H, 7·1. Calc. for $C_{10}H_{16}O_5$: C, 55·6; H, 7·4%). Its semicarbazone had m. p. 98°.

Ethyl αα-dimethyloxaloacetate was prepared by hydrolysis [20] of ethyl αα-dimethylethoxaloacetate (10 ml.) with concentrated hydrochloric acid (80 ml.) during 3 days. The oily product slowly deposited crystals (3 g.) (Found: C, 51·0; H, 6·5. Calc. for $C_8H_{12}O_5$: C, 51·0; H, 6·4%).

Pyruvic acid (B.D.H.) was distilled twice and then frozen (m. p. 13°) [Found (by titration against alkali): *M*, 88·2. Calc. for $C_3H_4O_3$: *M*, 88·1]. Only freshly prepared aqueous solutions were used.

Spectrophotometric Measurements.—A Hilger Uvispek spectrophotometer was used. Measurements on stable solutions were made in a cell compartment maintained by circulating water at 25°. Kinetic runs were made at room temperature (20°). Pairs of 1-cm. quartz cells were used, one of which contained the organic substrate, the concentration of the other components being identical in the two cells. In kinetic experiments optical-density measurements were begun 45 sec. after addition of the metal solution.

Potentiometric Measurements.—pH measurements were made with a Cambridge bench-type pH meter and a commercial glass electrode at 25°.

Microanalyses were carried out by Mr. J. M. L. Cameron.

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CHEMISTRY DEPARTMENT, THE UNIVERSITY, GLASGOW. [*Received, January 23rd*, 1958.]

[20] Rassow and Bauer, *J. praht. Chem.*, 1909, **80**, 87.

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737. *The Interaction of Transition-metal Ions with Oxaloacetic Acid. Part II.*[1] *Thermodynamics of Chelation.*

By E. GELLES and A. SALAMA.

The association of the bivalent ions of calcium, manganese, cobalt, nickel, copper, and zinc with oxaloacetic acid in aqueous solution at 25° has been studied potentiometrically. Thermodynamic equilibrium constants have been derived for reactions of the type $M^{2+} + A^{2-} \rightleftharpoons MA$, and evidence has also been obtained for the association $M^{2+} + MA \rightleftharpoons M_2A^{2+}$.

THE stabilities of the chelate compounds formed by transition-metal ions with oxaloacetic acid are of interest in connection with the catalysis of decarboxylation by these ions. Studies on the nature of the chelate compounds, and the mechanism of the decarboxylation catalysed by metal ions are described in the preceding paper.[1] A value for the association constant of copper oxaloacetate has already been derived indirectly from kinetic measurements.[2] Equilibrium constants for the association of rare-earth ions with oxaloacetic acid were obtained directly from potentiometric measurements,[3] and this method has now been applied to the ions of the first transition series.

[1] Part I, preceding paper.
[2] Pedersen, *Acta Chem. Scand.*, 1952, **6**, 285.
[3] Gelles and Nancollas, *Trans. Faraday Soc.*, 1956, **52**, 98.

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Experimental

The pH of solutions of transition-metal oxaloacetates was measured with a glass electrode in the cell:

$$\text{Ag} \,|\, \text{AgCl, HCl (0·2N)} \,|\, \text{glass} \,|\, \text{soln. under study} \,|\, \text{saturated KCl} \,|\, \text{calomel.}$$

The glass electrode was made from Corning 015 glass and had a resistance of 20 megohms. Potentials were measured on a Tinsley potentiometer reading to 0·05 mv, a valve voltmeter being used as null-point indicator. The electrode system was standardised with standard buffer solutions: 0·01M-hydrochloric acid, 0·09M-potassium chloride, pH = 2·078; 0·05M-potassium hydrogen phthalate, pH = 4·005; and B.D.H. tabloid phosphate buffer, pH = 6·99 at 25°. The factor for converting e.m.f. into pH was constant over the whole buffer range. The calomel electrode and a beaker, containing the glass electrode and fitted with a stirrer, were mounted in a water bath kept at 25° ± 0·1°.

A weighed quantity of oxaloacetic acid was dissolved in water containing a known amount of hydrochloric acid or sodium hydroxide, and the solution (50 ml.) introduced into the cell. After 2 min. metal chloride solution (1—4 ml.) was added, and the e.m.f. was noted at 1 min. intervals for about 10 min. The decarboxylation of oxaloacetic acid in the presence of transition-metal ions produced a slow drift in e.m.f., and values were extrapolated to the time of mixing with an accuracy of about ±0·2 mv. Chelation is known to be very fast.[1]

The purity of oxaloacetic acid was estimated by titration against alkali (Found: *M*, 132·6. Calc. for $C_4H_4O_5$: *M*, 132·1). Standard solutions of metal chlorides were prepared from "AnalaR" chloride or oxide and hydrochloric acid, and the strength was always checked gravimetrically.

Results

(The symbolism used here is the same as in Part I, preceding paper.)

Potentiometric measurements were carried out over a range of pH and metal-ion concentration. Within this range the measurements with copper oxaloacetate could be interpreted quantitatively in terms of one association equilibrium:

$$M^{2+} + A^{2-} \rightleftharpoons MA; \qquad K_{MA} = \{MA\}/\{M^{2+}\}\{A^{2-}\} \quad . \quad . \quad . \quad . \quad (1)$$

For other transition-metal ions the values of K_{MA}, calculated on the assumption of only one association equilibrium, varied with concentration of metal ion in such a way as to indicate that there was a small association of a second cation:

$$M^{2+} + MA \rightleftharpoons M_2A^{2+}; \qquad K_{M_2A^{2+}} = \{M_2A^{2+}\}/\{M^{2+}\}\{MA\} \quad . \quad . \quad . \quad (2)$$

On the basis of equilibria (1) and (2) we have, for the total concentration of metal ion

$$c_m = [M^{2+}] + [MA] + 2[M_2A^{2+}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

for the total concentration of oxaloacetic acid

$$c_a = [H_2A] + [HA^-] + [A^{2-}] + [MA] + [M_2A^{2+}] \quad . \quad . \quad . \quad . \quad (4)$$

and for electroneutrality ($[OH^-] \ll [H^+]$)

$$[H^+] + 2[M^{2+}] + 2[M_2A^{2+}] + [Na^+] = 2[A^{2-}] + [HA^-] + [Cl^-] \quad . \quad . \quad (5)$$

The first and the second ionisation constant of oxaloacetic acid at 25° are [4]

$$K_1 = \{HA^-\}\{H^+\}/\{H_2A\} = 2{\cdot}79 \times 10^{-3} \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

$$K_2 = \{A^{2-}\}\{H^+\}/\{HA^-\} = 4{\cdot}27 \times 10^{-5} \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

The ionic strength I is given by the equation;

$$I = \tfrac{1}{2}\left[[Na^+] + [Cl^-] + [H^+] + [HA^-] + 4[A^{2-}] + 4c_m - 4v\right] \quad . \quad . \quad (8)$$

where

$$v = c_a - [H_2A] - [HA^-] - [A^{2-}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

Assuming a value for the ionic strength, we can calculate the ionic activity coefficient f_1; a value for $[H^+]$ can then be obtained from the measured pH.

[4] Pedersen, *Acta Chem. Scand.*, 1952, **6**, 243.

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From eqns. (3)—(6) we have

$$[H_2A] = u/[2 + K_1/\{H^+\}f_1] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

where

$$u = [Cl^-] + 2c_a - 2c_m - [Na^+] - [H^+] \quad . \quad . \quad . \quad . \quad . \quad (11)$$

$[HA^-]$, $[A^{2-}]$, and $\{A^{2-}\}$ can be calculated from $[H_2A]$ and eqns. (6) and (7).

The ionic strength, I, and hence the activity coefficients, are obtained by successive approximations, two such approximations usually being sufficient.

The unknown association constants K_{MA} and $K_{M_2A^{2+}}$ are then obtained from the series of pH measurements by a graphical method

$$A = (B + CK_{M_2A^{2+}})\,K_{MA} - K_{MA}^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

where

$$A = v/\left((c_m - v)[A^{2-}]^2 f_2^4\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

$$B = c_m/\left((c_m - v)[A^{2-}] f_2^2\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

and

$$C = (c_m - 2v)^2/\left((c_m - v)[A^{2-}] f_2^2\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

A, B, and C can be calculated for each experiment from the known initial concentrations and the values of $[H_2A]$, $[HA^-]$, and $[A^{2-}]$. When the correct value of $K_{M_2A^{2+}}$ is chosen, a plot of A against $(B + CK_{M_2A^{2+}})$ will give a straight line of slope K_{MA} and intercept $-K_{MA}^2$.

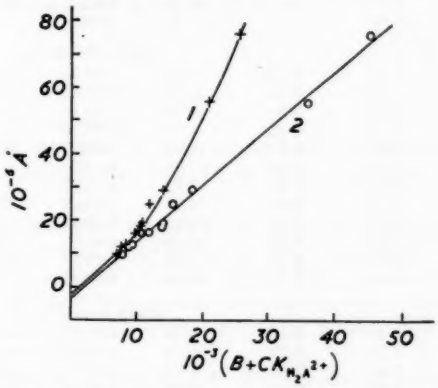

FIG. 1. *Zinc oxaloacetate.*
(1) $K_{M_2A^{2+}} = 0$.
(2) $K_{M_2A^{2+}} = 2 \times 10^2$.

Details of the pH measurements and the calculated parameters A, B, and C are given in Table 1.

Fig. 1 shows plots of A against $(B + CK_{M_2A^{2+}})$ for the experiments on zinc oxaloacetate. If only one complex of the type MA were formed, $K_{M_2A^{2+}}$ would be zero and a plot of A against B should give a straight line of slope K_{MA} and intercept $-K_{MA}^2$. In fact, when $K_{M_2A^{2+}}$ is taken as zero, a curve is obtained. Plots for assumed values of $K_{M_2A^{2+}} = 0$ and 2×10^2 are illustrated. Table 2 gives the values of K_{MA} obtained for different assumed values of $K_{M_2A^{2+}}$ and a comparison of $-K_{MA}^2$ and the intercept. It may be seen that $K_{M_2A^{2+}} = 2 \times 10^2$ fits the experimental results, giving a value of $K_{MA} = 1{\cdot}7 \times 10^3$.

A plot of A against B for the experiments on copper oxaloacetate gives a straight line of slope $K_{MA} = 7{\cdot}5 \times 10^4$ and intercept $-5{\cdot}6 \times 10^9 = -K_{MA}^2$. The results can therefore be accounted for quantitatively in terms of one association equilibrium. The value of K_{MA} at 37° has also been obtained indirectly from kinetic data on the decarboxylation catalysed by copper ions.[2] From experiments at ionic strengths 0·05 and 0·100 a value of $9{\cdot}7 \times 10^4$ at 37° was derived; with a reasonable estimate of the entropy change in the association reaction this value is reduced to about $7{\cdot}5 \times 10^4$ at 25°.

For nickel and cobalt ions, the two association constants fitting the results were determined similarly. There is a greater scatter of the experimental points in the experiments with manganese and calcium ions. With these the second association, if it occurs at all, has an association constant $K_{M_2A^{2+}}$ less than 10^2, but this cannot be more accurately defined, and there is therefore also a greater uncertainty in the values of K_{MA}.

TABLE 1. pH *measurements at* 25°.

10^3c_m	10^3c_a	10^3[Na^+]	10^3[Cl^-]	I	pH	$10^{-6}A$	$10^{-3}B$	$10^{-3}C$
			Zinc oxaloacetate					
1·94	7·35	6·72	4·12	0·0122	3·179	9·89	7·08	0·0029
1·94	7·43	6·16	4·12	0·0120	3·081	12·55	8·42	0·0048
1·94	7·18	5·32	4·12	0·0115	2·993	16·29	10·30	0·0077
3·81	7·31	7·69	8·08	0·0172	3·216	12·07	7·78	0·0060
3·81	7·13	6·59	8·08	0·0169	3·084	16·39	9·87	0·0036
3·81	7·24	6·32	8·08	0·0169	3·034	18·29	10·75	0·0150
3·81	7·24	6·32	8·08	0·0169	3·031	19·03	10·89	0·0150
3·81	7·16	6·04	8·08	0·0166	2·993	24·87	12·23	0·0164
3·81	7·17	5·50	8·08	0·0165	2·926	29·11	14·05	0·0220
7·34	6·99	5·82	15·55	0·0264	2·856	55·80	20·85	0·0746
7·34	6·78	5·03	15·55	0·0261	2·788	76·08	25·43	0·0990
			Copper oxaloacetate					
1·96	7·32	2·80	4·12	0·0079	2·533	2817	114	0·030
1·96	7·34	—	4·12	0·0079	2·362	3552	119	0·000
1·96	7·27	—	5·52	0·0090	2·279	6831	166	0·001
1·96	7·28	—	6·92	0·0104	2·218	7283	176	0·021
3·85	7·14	—	8·08	0·0125	2·294	6717	167	0·022
3·85	7·24	—	9·45	0·0141	2·234	8160	189	0·006
3·85	7·13	—	10·83	0·0152	2·166	13,200	241	0·086
7·41	6·87	—	16·88	0·0240	2·183	15,130	279	0·254
7·41	6·86	—	18·20	0·0254	2·132	18,660	318	0·614
			Nickel oxaloacetate					
1·92	7·22	6·72	4·04	0·0111	3·137	29·89	10·98	0·0002
1·92	7·35	6·16	4·04	0·0111	3·044	33·44	11·91	0·0013
1·92	7·31	5·60	4·04	0·0110	2·983	33·45	12·49	0·0034
1·92	7·32	5·04	4·04	0·0110	2·926	28·94	12·78	0·0072
3·77	7·27	6·59	7·92	0·0157	2·998	47·13	14·71	0·0071
3·77	7·20	6·04	7·92	0·0157	2·948	47·94	15·48	0·0117
3·77	7·21	5·49	7·92	0·0157	2·888	55·50	17·33	0·0170
3·77	7·09	4·95	7·92	0·0157	2·846	58·98	18·79	0·0235
7·26	6·93	5·82	15·26	0·0253	2·824	102·9	25·58	0·0689
7·26	6·93	5·82	15·26	0·0253	2·780	110·0	27·62	0·0849
7·26	6·87	4·76	15·26	0·0252	2·730	141·4	31·88	0·1028
7·26	6·93	4·23	15·26	0·0252	2·678	169·6	35·91	0·1237
			Cobalt oxaloacetate					
1·96	7·40	6·72	4·12	0·0126	3·201	6·01	6·06	0·0041
1·96	7·32	5·32	4·12	0·0116	2·984	14·98	10·16	0·0084
3·85	7·15	7·69	8·09	0·0175	3·276	8·50	6·68	0·0061
3·85	7·22	6·59	8·09	0·0174	3·112	10·26	8·48	0·0140
3·85	7·16	6·04	8·09	0·0170	3·027	15·92	10·59	0·0177
3·85	7·13	5·22	8·09	0·0166	2·915	25·61	14·00	0·0257
7·42	6·93	5·82	15·58	0·0266	2·883	46·88	19·38	0·0721
7·42	6·91	5·03	15·58	0·0265	2·806	57·20	23·02	0·0972
			Manganese oxaloacetate					
1·96	7·35	7·56	4·12	0·0137	3·398	1·97	3·72	0·0031
1·96	7·36	6·72	4·12	0·0132	3·249	2·21	4·76	0·0057
3·85	7·26	7·42	8·08	0·0183	3·277	4·07	5·49	0·0097
3·85	7·30	6·59	8·08	0·0181	3·148	4·67	6·90	0·0161
3·85	7·20	6·04	8·08	0·0177	3·072	6·44	8·37	0·0203
7·41	6·94	7·14	15·56	0·0285	3·180	5·43	7·92	0·0384
7·41	6·90	7·14	15·56	0·0281	3·160	7·56	8·70	0·0387
7·41	6·97	5·82	15·56	0·0283	3·002	9·14	11·36	0·0669
			Calcium oxaloacetate					
2·01	7·42	9·80	4·21	0·0165	3·847	0·619	1·81	0·0009
2·01	7·41	8·96	4·21	0·0152	3·667	1·077	2·41	0·0012
2·01	7·31	7·56	4·21	0·0142	3·427	1·129	3·27	0·0038
3·93	7·25	9·62	8·25	0·0212	3·761	0·712	2·20	0·0036
3·93	7·25	8·79	8·25	0·0205	3·599	0·927	2·76	0·0056
3·93	7·14	8·24	8·25	0·0203	3·527	0·849	3·02	0·0094
3·93	7·28	7·42	8·25	0·0195	3·329	1·563	4·42	0·0118
7·58	6·87	8·46	15·90	0·0298	3·442	2·32	4·72	0·0208
7·58	6·89	7·94	15·90	0·0299	3·364	2·23	5·23	0·0267
7·58	6·89	7·14	15·90	0·0297	3·234	2·65	6·64	0·0382
7·58	6·99	6·61	15·90	0·0293	3·121	4·24	8·60	0·0502

TABLE 2. *Solution for K_{MA} and $K_{M_2A}^{2+}$: zinc oxaloacetate.*

$10^{-2}K_{M_2A}^{2+}$ (assumed)	0	1	1·5	2	3
Slope of $10^{-2}K_{MA}$	curve	2·24	1·88	1·70	1·15
$-10^{-6}K_{MA}^2$	—	−5·0	−3·5	−2·9	−1·3
Intercept	—	−7·5	−4·5	−3·0	+2·5

With calcium and manganese ions the uncertainty in K_{MA} may be of the order of 20%, while the association constants for the other metal ions are accurate to about ±10%. Only orders of magnitude could be determined for the association constants $K_{M_2A}^{2+}$.

It has been assumed that activity coefficients of the chelate compounds are governed by the net charge. For example, those of type MA are taken as having an activity coefficient of one, although there is certainly some charge separation. The metal oxaloacetates were all studied over the same range of ionic strength. The association constant for copper oxaloacetate calculated on the basis of only one association equilibrium shows no trend with ionic strength. A comparison of the results with those for zinc, cobalt, and nickel oxaloacetate shows that the association of the second metal ion is a specific effect, which cannot be accommodated by making different assumptions about activity coefficients. The relative values of the association constants will not be greatly affected by use of different expressions for the variation of activity coefficients with ionic strength.[3] The association constants are listed in Table 3.

TABLE 3. *Thermodynamic association constants at 25°.*

	Ca^{2+}	Mn^{2+}	Co^{2+}	Zn^{2+}	Ni^{2+}	Cu^{2+}
$10^{-2}K_{MA}$	0·4	0·7	1·4	1·7	3·2	75
$10^{-2}K_{M_2A}^{2+}$	<1	<1	2	2	1·5	—

DISCUSSION

The upper limit to the range of concentration of metal ion and pH studied was set by the rate of decarboxylation. Above this limit the drift of e.m.f. with time was too rapid to permit accurate back-extrapolation.

Even at the lowest pH used no evidence for the species MAH^+ was obtained. This species can make a contribution to the rate of decarboxylation at a lower pH,[5] but the thermodynamic tendency for its formation, $M^{2+} + HA^- \rightleftharpoons MAH^+$, is clearly much smaller than for the reaction $M^{2+} + A^{2-} \rightleftharpoons MA$, mainly because the latter association involves a much greater increase of entropy. The concentration of MAH^+ must be very small under the present experimental conditions.

In the pH range of the potentiometric measurements the chelate compounds are predominantly of structure A.

A Oxaloacetate, MA

B

Evidence for this is discussed in the preceding paper. The proportion of enolic oxaloacetate complex B has been determined,[1] and does not appear to vary with pH in the low pH range studied. The association constants listed in Table 3 refer to any structure of type MA, either the ketonic complex A or the enolic complex B. The proportion of enolic complex is greatest for copper oxaloacetate (40%). The association constant for the ketonic complex should therefore be about 40% less than the overall association constant of $7·5 \times 10^4$ given in Table 3. A value of $4·5 \times 10^4$ would be close to that found for the association constant of copper αα-dimethyloxaloacetate.[1]

The catalytic effect of metal ions in the decarboxylation of oxaloacetic acid is related to the degree of interaction of the metal ions with oxaloacetate in the initial state and in

[5] Gelles and Salama, following paper.

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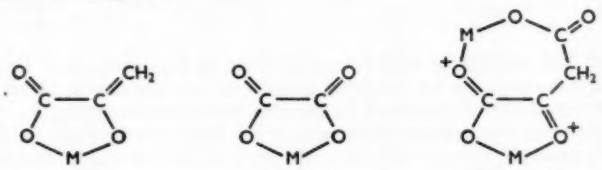
the transition state of decarboxylation.[5] The interaction in the transition state may resemble that in metal oxalates, and the association constants of oxaloacetates and oxalates are therefore compared.[6,7]



α-Oxocarboxylate complexes should have lower association constants than dicarboxylates of the same ring size. This is borne out by the data in Table 4. There is a general parallelism between the association constants for oxaloacetates and oxalates,

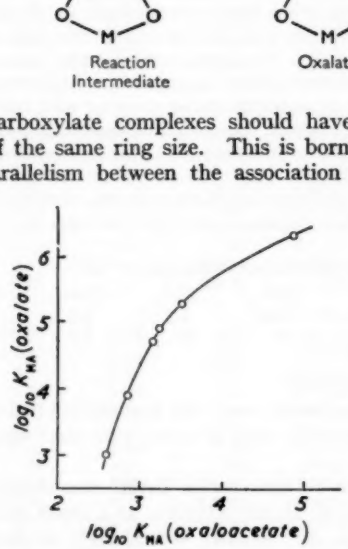


FIG. 2. *Association constants for oxaloacetates and oxalates.*

but Fig. 2 shows that association constants for nickel and copper oxalates are low compared with those for the oxaloacetates. This would still be true if the comparison were made with the reduced association constants for the ketonic oxaloacetate complexes.

TABLE 4. $\log_{10} K_{MA}$ *for oxaloacetates, oxalates, and succinates.*

	Ca^{2+}	Mn^{2+}	Co^{2+}	Zn^{2+}	Ni^{2+}	Cu^{2+}
Oxaloacetate	2·6	2·8	3·1	3·2	3·5	4·9
Oxalate	3·0	3·9	4·7	4·9	5·3	6·3
Succinate	1·9	—	—	2·5	—	3·3

The lowering of association constant with increasing ring size is illustrated by data on some succinates.[8] Association constants for the oxaloacetate complexes M_2A^{2+} are given in Table 3. No evidence for Cu_2A^{2+} was found in the concentration range examined, but this could be due to a greater difference between the values of K_{MA} and $K_{M_2A^{2+}}$. The complexes M_2A^{2+} have association constants of the same order of magnitude as those for seven-membered ring succinates. The most likely structure for the species M_2A^{2+} is one involving a seven-membered ring compound, in which the two metal ions are competing for electrons. This could give rise to the observed variation in the values of $K_{M_2A^{2+}}$ as the complexing power of the metal ion increases from Ca^{2+} to Cu^{2+}. Oxalate complexes of type M_2A^{2+} have been studied.[9]

CHEMISTRY DEPARTMENT, THE UNIVERSITY, GLASGOW. [*Received, January 23rd,* 1958.]

[6] Money and Davies, *Trans. Faraday Soc.*, 1932, **28**, 609.
[7] Ives, *J.*, 1933, 1360.
[8] Irving, Williams, Ferrett, and Williams, *J.*, 1954, 3494.
[9] Vosburgh and Beckman, *J. Amer. Chem. Soc.*, 1940, **62**, 1028.

738. *The Interaction of Transition-metal Ions with Oxaloacetic Acid. Part III.* Kinetics of the Catalysed Decarboxylation.*

By E. Gelles and A. Salama.

The kinetics of decarboxylation of oxaloacetic acid in the presence of bivalent ions of calcium, manganese, cobalt, nickel, and zinc have been studied manometrically. Catalysis and inhibition of the reaction are related to the nature and stability of the chelate compounds formed under different conditions.

Quantitative studies of the kinetics of decarboxylation of oxaloacetic acid have shown that the undissociated acid and the two anions undergo first-order decomposition,[1,2] and that catalysis by metal ions can be related to the formation of a chelate compound, which also loses carbon dioxide in a first-order reaction.[3] A study of the reactions catalysed by copper and zinc ions indicated that the catalytically important species was a compound of the type MA, where M^{2+} and A^{2-} represent metal and substrate ions.[1] The catalytic power of transition-metal ions in the decomposition of acetonedicarboxylic acid follows the thermodynamic stability of the corresponding malonates.[4] A similar correlation has been established between the catalytic effect of rare-earth ions in the decarboxylation of oxaloacetic acid and the stability of chelate compounds of rare-earth oxaloacetates.[5] These studies have been extended to the metal ions of the first transition series. Thermodynamic association constants have been obtained,[6] and catalytic rate coefficients have now been measured.

Experimental

Weighed samples of oxaloacetic acid were dissolved in the requisite amounts of water, standard hydrochloric acid, and potassium chloride solution. After addition of the metal chloride solution, the reaction mixture (5 ml.) was run into the gas-evolution apparatus, which was evacuated, sealed, and placed in a water thermostat maintained at 36·9° ± 0·03°. Decarboxylation was then followed manometrically as previously described.[5] With very fast reactions a modified apparatus was used. A magnetically operated plunger supported a bucket containing oxaloacetic acid above the appropriate solution. The apparatus was evacuated and sealed, and the reaction was started by withdrawing the plunger into a sidearm. An oxaloacetic acid concentration of 0·03M produced a suitable rise in the mercury manometer. 80—90% of reaction was generally followed and the rate coefficients were obtained from first-order plots, the infinity readings being taken after 10 half-times of reaction. " AnalaR " materials and " grade A " volumetric glassware were used.

Results and Discussion

A series of experiments were designed to study the kinetic behaviour of the chelate compounds MA. In the range of pH and metal-ion concentration used the concentration of the species MAH^+ is small, as indicated [6] potentiometrically; however, a kinetic contribution from this species could be detected in some cases.

Catalysis.—In the appropriate concentration range the rate of decarboxylation is given by the equation

$$d[CO_2]/dt = -dc_a/dt = k_u c_a + k[MA] + k'[MAH^+] \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where k_u, k, k' are first-order rate coefficients.

This equation is applied when the concentration of chelate compound is so small that the

* Part II, preceding paper.

[1] Pedersen, *Acta Chem. Scand.*, 1952, **6**, 285.
[2] Gelles, *J.*, 1956, 4736
[3] Gelles and Hay, *ibid.*, 1958, 3673.
[4] Prue, *ibid.*, 1952, 2331.
[5] Gelles and Clayton, *Trans. Faraday Soc.*, 1956, **52**, 353.
[6] Gelles and Salama, preceding paper.

concentration of free metal ion can be taken as equal to the total concentration of metal, c_m, and the concentration of free oxaloacetate as equal to the total concentration of oxaloacetic acid, c_a.

α_1 and α_2, the degrees of dissociation of oxaloacetic acid into the ions HA^- and A^{2-} respectively, are given by the equations

$$\alpha_1/(1 - \alpha_1 - \alpha_2) = K_1^c/[H^+], \text{ and } \alpha_2/(1 - \alpha_1 - \alpha_2) = K_1^c K_2^c/[H^+]^2 \quad . \quad . \quad (2)$$

where $K_1^c (= 6{\cdot}19 \times 10^{-3})$ and $K_2^c (= 1{\cdot}37 \times 10^{-4})$ are the concentration ionisation constants of oxaloacetic acid [1] at ionic strength 0·1. The concentration association constants at ionic strength 0·1 are defined by the equations

$$K_{MA}^c = [MA]/[M^{2+}][A^{2-}] \text{ and } K_{MAH^+}^c = [MAH^+]/[M^{2+}][HA^-] \quad . \quad . \quad . \quad (3)$$

Then, from eqns. (1) and (3) we obtain

$$d[CO_2]/dt = k_u c_a + kK_{MA}^c[M^{2+}][A^{2-}] + k'K_{MAH^+}^c[M^{2+}][HA^-] \quad . \quad . \quad . \quad (4)$$

and by substitution for $[A^{2-}]$ and $[HA^-]$ from eqns. (2)

$$k_{obs} = k_u + kK_{MA}^c c_m (K_2^c \alpha_1/[H^+]) + k'K_{MAH^+}^c c_m \alpha_1 \quad . \quad . \quad . \quad . \quad . \quad (5)$$

where k_{obs} is the observed first-order rate coefficient. Hence

$$(k_{obs} - k_u)/(K_2^c \alpha_1 c_m) = kK_{MA}^c[H^+]^{-1} + k'K_{MAH^+}^c/K_2^c \quad . \quad . \quad . \quad . \quad . \quad (6)$$

A plot of $(k_{obs} - k_u)/(K_2^c \alpha_1 c_m)$ against $[H^+]^{-1}$ will give a straight line of slope kK_{MA}^c and intercept $k'K_{MAH^+}^c/K_2^c$.

TABLE 1. *Rate coefficients for the uncatalysed reaction.*

(Concentrations are in moles/l.; $10^2 c_a = 3{\cdot}00$.)

10^2[HCl]	0·255	0·500	1·00	2·00	2·50	5·00
10^2[H$^+$]	1·23	1·39	1·75	2·56	2·99	5·30
α_1	0·334	0·307	0·261	0·1945	0·1715	0·1048
α_2	0·00373	0·00303	0·00200	0·00104	0·00079	0·00027
$10^4 k_u$ (sec.$^{-1}$)	0·91	0·84	0·725	0·555	0·495	0·325

TABLE 2. *Catalysis by transition metal ions at* 36·9°.

($c_a = 0{\cdot}03$, $I = 0{\cdot}1$.)

			Zn^{2+}					
10^2[H$^+$]	1·39	1·39	1·75	1·75	2·99	2·99	5·30	
$10^3 c_m$	5	7·5	5	10	10	20	15	
$10^4 k_{obs}$	1·98	2·65	1·48	2·18	1·08	1·80	0·672	
R	542	574	422	407	249	278	161	
			Ni^{2+}					
10^2[H$^+$]	1·75	1·75	2·56	2·56	2·99	2·99	5·30	5·30
$10^3 c_m$	5	10	5	10	10	20	10	15
$10^4 k_{obs}$	1·86	2·88	1·13	1·73	1·38	2·21	0·649	0·851
R	636	602	432	441	377	365	226	244
			Co^{2+}					
10^2 [H$^+$]	1·75	1·75	2·56	2·56	2·99	2·99	5·30	
$10^3 c_m$	5	15	10	20	10	20	15	
$10^4 k_{obs}$	1·25	2·30	1·11	1·65	0·874	1·36	0·576	
R	294	294	208	205	161	184	117	
			Mn^{2+}					
10^2[H$^+$]	1·23	1·23	1·23	1·23	1·39	1·39	1·39	
$10^3 c_m$	15	20	25	25	15	20	25	
$10^4 k_{obs}$	1·31	1·42	1·54	1·57	1·11	1·21	1·28	
R	58·2	55·8	55·0	57·6	42·8	44·0	41·8	
10^2[H$^+$]	1·75	1·75	2·99	2·99	2·99	5·30		
$10^3 c_m$	15	20	20	20	20	15		
$10^4 k_{obs}$	0·94	1·00	0·585	0·595	0·600	0·347		
R	39·6	38·5	19·3	21·3	22·4	10·2		
			Ca^{2+}					
10^2[H$^+$]	1·23	1·23	1·39	1·39	1·75	1·75	2·99	2·99
$10^3 c_m$	25	25	15	20	20	25	10	20
$10^4 k_{obs}$	1·025	1·045	0·908	0·921	0·790	0·805	0·504	0·522
R	10·1	11·8	10·8	9·6	9·1	8·95	5·1	5·7

The measurement of rate coefficients for the uncatalysed reaction, and the calculation of α_1, α_2, and k_u have been described.[1,2] The relevant data on the uncatalysed reactions at ionic strength 0·1 are collected in Table 1. The values of α_1, α_2, $[H^+]$, and k_u will be unchanged in the presence of metal ions if $[M^{2+}]$ can be taken as equal to c_m. Potentiometric data indicate the concentration range in which this assumption is justified.[6]

The kinetic data for catalysis by transition-metal ions are summarised in Table 2. The quantity $(k_{obs} - k_u)/(K_2^c\alpha_1 c_m)$ is represented by R, and is calculated by using the values of α_1 and k_u given in Table 1.

Figs. 1 and 2 show plots of R against $1/[H^+]$. Individual rate coefficients are known with an accuracy of ± 2—3%, but R involves a difference $(k_{obs} - k_u)$, which becomes quite small for catalysis by manganese and calcium ions. In view of this the linearity of the plots can be considered very satisfactory. No systematic variation of R with concentration of metal ion could be detected, at any given concentration of hydrogen ion. This supports the prediction from the known [6] association constants, that $[M^{2+}] \sim c_m$ under the present conditions. The small positive intercepts on the ordinate indicate that the species MAH^+ makes some kinetic

FIG. 1. *Catalysis*: (1) Ni^{2+}, (2) Zn^{2+}, (3) Co^{2+}.

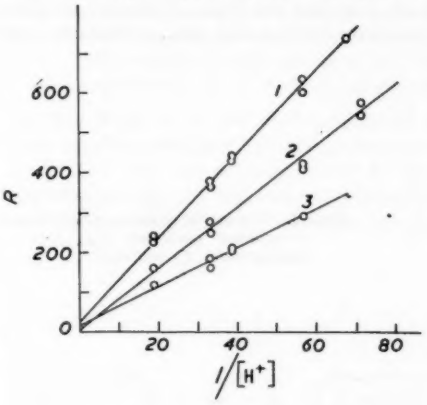
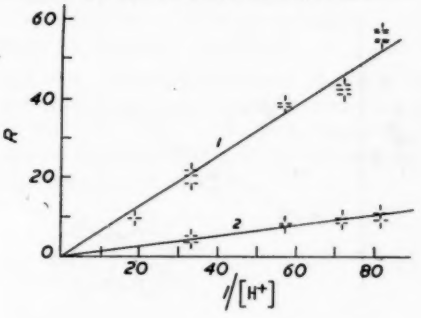


FIG. 2. *Catalysis*: (1) Mn^{2+}, (2) Ca^{2+}.



contribution to the rate of decarboxylation. The coefficients kK_{MA}^c for the species MA are obtained from the slope of these plots. The thermodynamic association constants at 25°, K_{MA}, have been measured.[6] The concentration association constants K_{MA}^c at 36·9° and ionic strength 0·1, can be estimated from activity coefficients calculated from the Davies equation, and a constant entropy of association calculated from thermodynamic data on copper oxaloacetate at 37° [1] and 25° [6]: It is found that $K_{MA}^c \approx 0{\cdot}143\ K_{MA}$. The rate coefficients kK_{MA}^c, and approximate rate constants k for decarboxylation of the chelate compounds MA are given in Table 3.

TABLE 3. *Rate constants for chelate compounds* MA *at* 36·9° *and ionic strength* $I = 0{\cdot}1$.

	Ca^{2+}	Mn^{2+}	Co^{2+}	Zn^{2+}	Ni^{2+}	Cu^{2+}
kK_{MA}^c	0·14	0·65	4·8	7·6	10·7	706 [1]
10^2k (approx.)	0·24	0·65	2·4	3·1	2·3	6·6

In the study of catalysis by metal ions it is usual to determine the catalytic rate coefficient kK_{MA}^c. This coefficient provides a measure for the effect of metal ion on the rate of reaction; it is a composite measure of the concentration of chelate compounds formed (K_{MA}^c), and of their reactivity (k). A parallelism between the rate coefficients kK_{MA}^c and the association constants K_{MA}^c is to be expected and is indeed found.

Comparison can be made between the rate constants, k, and the association constants for oxaloacetates and oxalates listed in Table 4 of the preceding paper.

The association constants, K_{MA}^c, for the oxaloacetates refer to both ketonic and enolic form

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of the complex MA, and only the former undergoes decarboxylation. The proportion of enol has been determined [3] for each metal ion. The association constants corresponding to the formation of only the ketonic complex can thus be calculated. Division of the rate coefficients kK_{MA}^{c} (Table 3) by these ketonic association constants will give rate constants corresponding to the active ketonic complexes. However, the general conclusions from a comparison of rate constants and association constants are not altered by using constants for the active ketonic complex instead of the overall constants. Comparison will therefore be made between the overall rate constants given in Table 3 and the overall association constants.[6] It is seen that the rate constants k do not follow the order of association constants.

The interaction of metal ion and substrate in the transition state of decarboxylation might resemble that in the initial state (a). In that case a parallelism between rate constant and association constant for oxaloacetates would be expected

$$k = GK_{MA}^{\alpha} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

$$\log k = \alpha \log K_{MA} + \log G \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

or

$$\log kK_{MA} = (\alpha + 1) \log K_{MA} + \log G \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

Fig. 3 shows a logarithmic plot of the rate constants k against the thermodynamic association constants for oxaloacetates. It is seen that the reactivity of the nickel, and particularly of the

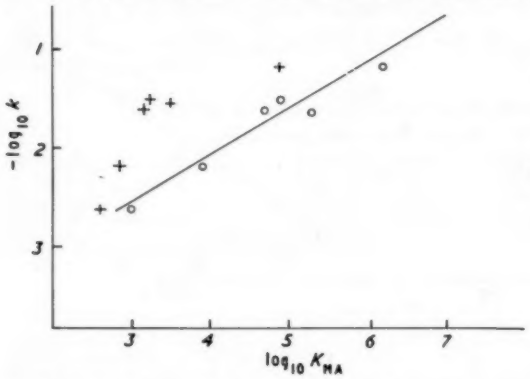

FIG. 3. *Variation of rate constants k with association constants K_{MA} for:* + *oxaloacetates,* ○ *oxalates.*

copper chelate compounds, is considerably lower than expected from a linear free energy relation. Allowance for the formation of a catalytically inactive enolic form does not change the relation significantly.

(a) (b)

If the transition state of reaction corresponds more closely to (b) than to (a) the interaction between metal ion and substrate should be similar to that in metal oxalates, which have considerably higher association constants than the oxaloacetates.[6]

A logarithmic plot (Fig. 3) of the rate constants k against the thermodynamic association constants for the oxalates is approximately linear. The two plots indicate the strength of the interaction of metal ion and substrate in the transition state of decarboxylation, which appears to resemble structure (b).

Inhibition.—There is potentiometric evidence for the formation of the chelate compounds M_2A^{2+} at high concentration of metal ion.[6] The structure of this complex is discussed in the preceding paper. The kinetics of decarboxylation at low concentrations of chelate compound could be interpreted without contribution from the species M_2A^{2+}; a significant retardation, observed at high concentrations of copper ion, is being investigated.

At high values of pH enols are formed which are not decarboxylated.[3] At pH 13, αα-dimethyloxaloacetic acid decomposes, but no carbon dioxide is evolved by oxaloacetate or copper oxaloacetate. Studies of the inhibition of this reaction are being continued.

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CHEMISTRY DEPARTMENT, THE UNIVERSITY, GLASGOW. [*Received, January 23rd*, 1958.

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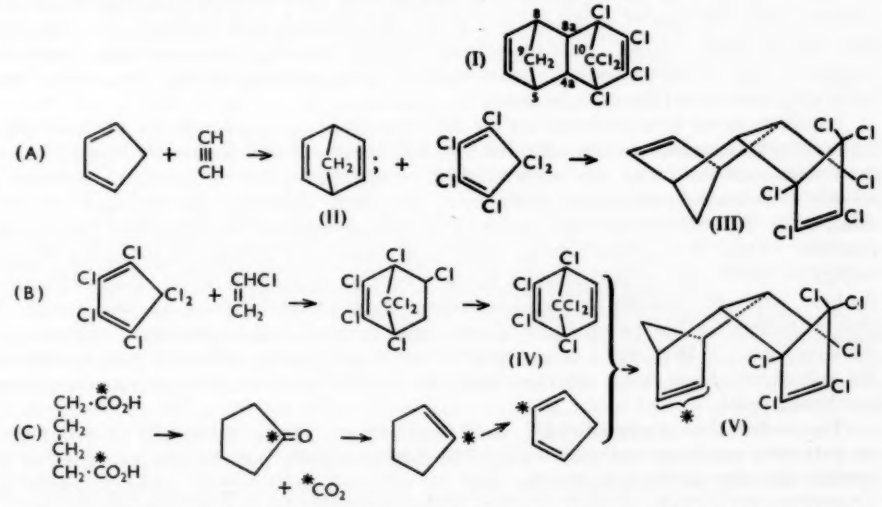
739. *The Synthesis of* ^{14}C-*Labelled* 1 : 2 : 3 : 4 : 10 : 10-*hexachloro*-6 : 7-*epoxy*-1 : 4 : 4*a* : 5 : 6 : 7 : 8 : 8*a*-*octahydro*-exo-1 : 4-exo-5 : 8-*dimethanonaphthalene* (*Endrin*).*

By G. T. BROOKS.

A study of the absorption, metabolism, and excretion of insecticides derived from decahydro-1 : 4 : 5 : 8-dimethanonaphthalene required a method for the preparation on a millimolar scale of such compounds labelled with ^{14}C. ^{14}C-Labelled endrin has now been synthesised by peracetic acid oxidation of ^{14}C-labelled isodrin prepared by Diels–Alder addition [1] of [2-^{14}C]*cyclo*pentadiene to 1 : 2 : 3 : 4 : 7 : 7-hexachloro*bicyclo*[2 : 2 : 1]hepta-2 : 5-diene.[2]

ALDRIN (1 : 2 : 3 : 4 : 10 : 10-hexachloro-1 : 4 : 4a : 5 : 8 : 8a-hexahydro-*exo*-1 : 4-*endo*-5 : 8-dimethanonaphthalene *) and its *exo,exo*-isomer isodrin, having the basic structure of 1 : 2 : 3 : 4 : 10 : 10 - hexachloro - 1 : 4 : 4a : 5 : 8 : 8a - hexahydro - 1 : 4 - 5 : 8 - dimethanonaphthalene (I), are represented stereochemically by formulæ (III) and (V), respectively, and the corresponding 6 : 7-epoxides are known as dieldrin and endrin.



As part of a research into the mechanism of insect resistance to insecticides, a method was required for synthesis, on a millimolar scale, of aldrin, or related compounds derived from decahydro-1 : 4-5 : 8-dimethanonaphthalene, labelled with ^{14}C.

* For name, see British Standard 1831: 1957. The numbering used is based on that of the Ring Index, No. 2229. The trivial names aldrin, isodrin, etc., are used here for convenience, though they normally refer to not quite pure materials.

[1] Bluestone, U.S.P. 2,676,132/1954.
[2] Kleiman, U.S.P. 2,655,513/1953.

Diels–Alder addition of acetylene to *cyclo*pentadiene [3,4] affords *bicyclo*[2 : 2 : 1]hepta-2 : 5-diene (II) which reacts (scheme A) with hexachloro*cyclo*pentadiene to give aldrin (III), while inclusion of the chlorine atoms in the dienophilic reactant (scheme B) leads to isodrin (V). Each synthesis requires two Diels–Alder additions in which diene, dienophile, or both might be labelled with ^{14}C. In either case ^{14}C-labelling of the intermediate dienophile (II or IV) involves Diels–Alder addition under conditions unfavourable to small-scale working and between components susceptible to decomposition. Thus, vinyl bromide (from acetylene) has been condensed with *cyclo*pentadiene to give dehydronorbornyl bromides, which with hexachloro*cyclo*pentadiene gave aldrin hydrobromides, subsequently dehydrobrominated to aldrin. A repetition of this synthesis on a millimolar scale with [^{14}C]acetylene gave no radio-active aldrin.[5]

An alternative approach, involving ^{14}C-labelling of the diene component only, requires the synthesis of hexachloro[^{14}C]*cyclo*pentadiene for scheme A or [^{14}C]*cyclo*pentadiene for scheme B. Krall [5] reports the use of trichloro[^{14}C]ethylene in the Prins synthesis [6] of hexachloro*cyclo*pentadiene, but the product, used in scheme A, gave no radioactive aldrin on a millimolar scale. The synthesis of [^{14}C]*cyclo*pentadiene would lead directly to isodrin (scheme B) and might lead, with suitable extension, to aldrin.

Synthesis of ^{14}C-labelled isodrin and endrin on a millimolar scale *via* [2-^{14}C]*cyclo*pentadiene (scheme C) is now reported.[7] [1-^{14}C]*cyclo*Pentanone, from [1 : 6-$^{14}C_2$]adipic acid by pyrolysis with barium hydroxide,[8] was reduced to [1-^{14}C]*cyclo*pentanol which afforded [1-^{14}C]*cyclo*pentene on dehydration. Bromination of the *cyclo*pentene gave 1 : 2-dibromo[1-^{14}C]*cyclo*pentane, which was then dehydrobrominated to [2-^{14}C]*cyclo*pentadiene. Diels–Alder condensation of [2-^{14}C]*cyclo*pentadiene with 1 : 2 : 3 : 4 : 7 : 7-hexachloro*bicyclo*[2 : 2 : 1]hepta-2 : 5-diene (IV) gave [^{14}C]isodrin. Oxidation of this product with peracetic acid in benzene [1] gave the corresponding 6 : 7-epoxide, endrin.

The pyrolysis of [1 : 6-$^{14}C_2$]adipic acid gave an 80% yield of *cyclo*pentanone containing half the initial ^{14}C (one ^{14}C atom was lost during pyrolysis) so that recovery of isotope was 40% on this stage. A 90% yield of *cyclo*pentanol was obtained from the crude ketone by reduction with aqueous sodium borohydride; [9] this avoided drying the ketone and facilitated isolation of the *cyclo*pentanol.

Liquid reagents were preferred for the dehydration of *cyclo*pentanol and, of these, 88% orthophosphoric acid regularly afforded 80—90% yields of *cyclo*pentene.[10] Quantitative bromination of the latter was accomplished *in vacuo*, at a low temperature without a solvent. Dehydrobromination procedures presented difficulty on account of the small scale of working and the tendency of *cyclo*pentadiene to polymerise during the reaction. Thus, the sodium acetate–acetic acid method of Zelinsky and Lewina [11] gave negligible yields of *cyclo*pentadiene from 0·1-molar quantities of 1 : 2-dibromo*cyclo*pentane, while the sodium hydroxide–ethylene glycol method [12] gave 20—30% yields of *cyclo*pentadiene on this scale but proved unsuitable for small-scale operations. 8-Hydroxyquinoline gave a 36% yield of *cyclo*pentadiene which readily afforded pure isodrin in the subsequent Diels–Alder reaction, and this method gave equally good results on the centimolar scale.

The isodrin thus produced (9·1% yield from adipic acid) was chemically identical with an authentic specimen and was shown to be radiochemically pure by the constancy of its specific activity on recrystallisation and by reversed-phase paper chromatography in

[3] Hyman, Freireich, and Lidov, B.P. 701,211/1953.
[4] Plate and Pryanishnikova, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 1956, 741.
[5] Krall, *Diss. Abs.*, 1957, **17**, 2421.
[6] Prins, *Rec. Trav. chim.*, 1950, **69**, 1003.
[7] Preliminary communication: Brooks, *Chem. and Ind.*, 1958, **7**, 194.
[8] Vogel, "Practical Organic Chemistry," Longmans, Green & Co., London, 2nd edn., 1951, p. 338.
[9] Chaikin and Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 122.
[10] Kogl and Ultée, *Rec. Trav. chim.*, 1950, **69**, 1576.
[11] Zelinsky and Lewina, *Ber.*, 1933, **66**, 477.
[12] Hine, Brown, Zalkow, Gardner, and Hine, *J. Amer. Chem. Soc.*, 1955, **77**, 594.

several solvent systems [13] with the authentic compound, located by the permanganate technique developed for pyrethroids.[14] The labelled compound was located on paper by radiometric scanning.[15]

From scheme C and the geometry of the diene addition the product is a mixture of [6-^{14}C]- and [7-^{14}C]-isodrin, though this designation makes no allowance for possible randomisation during the preparation of [^{14}C]*cyclo*pentadiene from [1-^{14}C]*cyclo*pentanol. Such randomisation, which might result in general labelling of the unchlorinated terminal five-membered ring in isodrin, has been observed previously during a reaction of [1-^{14}C]-*cyclo*pentanol involving an intermediate carbonium ion.[16]

Experimental

General.—Materials were of " AnalaR " grade where possible. For assay of ^{14}C, samples were mounted on 1·75 cm. diameter Whatman No. 1 filter circles impregnated with soya-bean oil (from a 3% v/v solution in ether) and counted under a thin-end-window Geiger–Müller tube under standardised conditions of geometry, taking the mean of pairs of counts made over both faces of the discs. The self-absorption correction was treated as constant since the weights of the discs did not vary appreciably and the weights of added solids were negligible.

Authentic samples of hexachloro*cyclo*pentadiene, isodrin, and endrin were kindly presented by Shell Research Ltd.

[1-^{14}C]cyclo*Pentanone*.—A mixture of adipic acid (2·24 g.) and [1 : 6-^{14}C$_2$]adipic acid (0·236 g., 5 millicuries, purchased from the Radiochemical Centre, Amersham) was dissolved in absolute ethanol (50 c.c.) by heat, the stirred solution evaporated to dryness, and the residue cooled in a desiccator. A sample (50 mg.) was dissolved in absolute ethanol (10 c.c.), and the solid from a 5 μl. portion of the solution, counted as indicated, gave 4475 counts/min.

An intimate mixture of the labelled adipic acid and barium hydroxide octahydrate (0·125 g.), contained in a small-scale pyrolysis apparatus, was heated to 290° during 90 min. and held at this temperature for 2½ hr.; a mixture of *cyclo*pentanone and water distilled into a receiver containing anhydrous potassium carbonate (0·5 g.), while labelled carbon dioxide (containing half the initial ^{14}C) was absorbed in bubblers containing aqueous 2N-sodium hydroxide. The mixture of water and *cyclo*pentanone was distilled at 0·1 mm. into a 50 c.c. flask, cooled to −196°, and weighed (1·25 g.). In experiments with inactive material the dried ketone had n_D^{20} 1·4364 (1·0—1·1 g.).

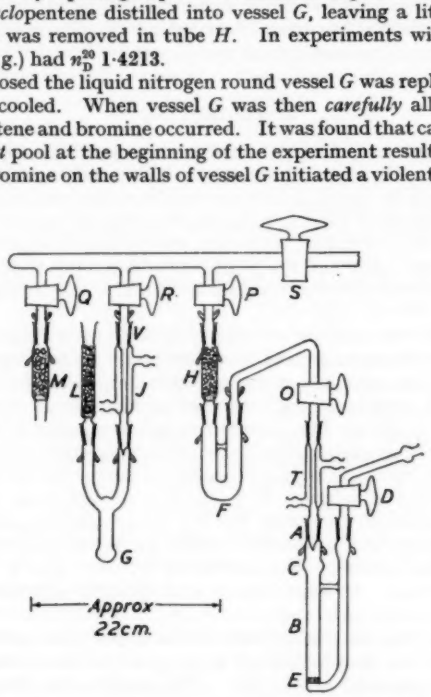
[1-^{14}C]cyclo*Pentanol*.—The wet *cyclo*pentanone was dissolved in water (10 c.c.) and reduced by gradual addition of sodium borohydride (0·45 g.) in water (5 c.c.) with cooling and swirling so that the temperature remained at 25—30°. The solution was then heated at 60—70° for 4 hr., cooled, saturated with potassium carbonate, and extracted three times with ether. The ethereal extracts were concentrated at 60° and moisture was removed from the liquid residue by successive addition and evaporation of methylene chloride (5 c.c. portions); complete removal of water was indicated by the appearance of solid inorganic salts in the vessel.

[1-^{14}C]cyclo*Pentene and* 1 : 2-*Dibromo*[1-^{14}C]cyclo*pentane*.—*cyclo*Pentanol (0·9—1·0 g.; n_D^{20} 1·4530 in inactive experiments) was distilled at 0·1 mm. into the bubbler *B* (see Figure) which was immersed in liquid nitrogen as far as bulb C. The distillate solidified at *C* and a slow stream of dry nitrogen admitted at *D* held the *cyclo*pentanol above the sintered plate *E* after removal of the coolant. 88% Orthophosphoric acid (1·5 c.c.) was added to the *cyclo*pentanol, and vessel *B* was connected to the vacuum manifold at *A*. The nitrogen admitted at *D* provided an inert atmosphere during the reaction and served both to stir the reactants and to sweep out *cyclo*pentene into the receiver *F*, cooled to −78°, during the subsequent dehydration. Receiver *F* was connected to the bromination tube *G via* the " Hidrite " tube *H* and condenser *J*. Drying tubes *L* and *M* contained calcium chloride. Before dehydration commenced, stopcocks *D*, *O*, *P*, and *Q* were open; *R* and *S* were closed. Bromine (0·7 c.c.) was placed in vessel *G* and frozen into a *neat* pool at −196°, a stopper replacing the drying tube *L*; tube *L* was replaced and vessel *G* immersed in a bath at −78°. Tap *R* was then opened and *Q* closed, so that nitrogen

[13] Mitchell, *J. Assoc. Off. Agric. Chem.*, 1953, **36**, 1183.
[14] Winteringham, Harrison, and P. M. Bridges, *Biochem. J.*, 1955, **61**, 359.
[15] Winteringham, Harrison, and R. G. Bridges, *Analyst*, 1952, **77**, 19.
[16] Lotfield, *J. Amer. Chem. Soc.*, 1951, **73**, 4709 (footnote).

entered the apparatus at *D* and left it at *L*. The oil-bath surrounding vessel *B* up to the level *C* was heated slowly to 120°, with hot water at 60—70° passing through condenser *T*; *cyclo*pentene distilled with the oil-bath at 120—125° and the temperature was allowed to rise to 140° after the reaction had apparently ceased. A stream of warm air directed on tap *O* assisted the transfer of *cyclo*pentene to trap *F*. Tap *O* was then closed and the nitrogen flow stopped. Tube *L* was replaced by a stopper, the baths round *F* and *G* were replaced by liquid nitrogen, and the apparatus was evacuated by opening tap *S*. When this tap *S* was closed and the coolant removed from trap *F*, *cyclo*pentene distilled into vessel *G*, leaving a little high-boiling residue; moisture in the product was removed in tube *H*. In experiments with inactive material the *cyclo*pentene (about 0·60 g.) had n_D^{20} 1·4213.

With taps *P* and *R* closed the liquid nitrogen round vessel *G* was replaced by a bath at −78°; condensor *J* was water-cooled. When vessel *G* was then *carefully* allowed to warm to about −8°, reaction of *cyclo*pentene and bromine occurred. It was found that careful condensation of the bromine into a small *neat* pool at the beginning of the experiment resulted in a smooth reaction; traces of uncondensed bromine on the walls of vessel *G* initiated a violent reaction which had to be



arrested by rapid cooling. Complete bromination was ensured by condensing traces of *cyclo*pentene vapour with liquid nitrogen and repeating the bromination. Excess of bromine was transferred to trap *F*, cooled to −196° with taps *P* and *R* open and vessel *G* immersed in water at 60° for 30—60 min.; the almost colourless dibromide weighed 2·42 g. (0·011 mol., 62% yield from adipic acid). Inactive product had n_D^{20} 1·5510. Zelinsky and Lewina [11] record n_D^{19} 1·5510.

Dehydrobromination of 1 : 2-*Dibromo*[1-^{14}C]cyclo*pentane and Synthesis of* [^{14}C]*Isodrin*.—The apparatus was a modification of that illustrated. Vessel *G*, containing 1 : 2-dibromo*cyclo*pentane (2·42 g.) and 8-hydroxyquinoline (4·5 g., 0·03 mol.) now replaced *B*; the connection between condenser *T* and trap *F* had no stopcock, and the outlet *V* carried a thick-walled tube, 17 × 1·7 cm., attached by a B.10 socket and capable of being sealed while attached to the vacuum-manifold.

With stopcocks other than *D*, *P*, and *Q* closed and receiver *F* cooled to −78°, a slow stream of nitrogen was admitted at *D* and the oil-bath round vessel *G* was heated slowly to 200°. Water at 70° passed through condenser *T* and a stream of warm air directed on the connection *T*–*F* assisted transfer of hydrocarbon to trap *F*. When the effervescence in vessel *G* had ceased, the temperature was raised slowly to 230°, then heating and nitrogen flow were stopped. The connection *T*–*F* was then removed and trap *F* closed by a stopper; finally taps *P* and *Q* were closed and trap *F* cooled to −196°. The tube attached at *V* and cooled to −196° contained *freshly* redistilled 1 : 2 : 3 : 4 : 7 : 7-hexachloro*bicyclo*[2 : 2 : 1]hepta-2 : 5-diene [1,2] (2·7 g.), prepared from hexachloro*cyclo*pentadiene, and a trace of quinol. With taps *P* and *R* open, the

apparatus was evacuated, tap *S* was closed, and the hydrocarbon transferred to the reaction tube which was then sealed off from the manifold.

The mixture was shaken, heated in an oven at 90° for 5 hr., then cooled, and the tube was broken while its contents were frozen at −196°. The almost colourless mixture was diluted with methanol–acetone (4 : 1) and cooled overnight at 0°. The crystals were collected, washed with methanol–acetone (4 : 1), drained, and dried at 1 mm. for 30 min. The product (0·57 g., 1·6 millimols.; 9% yield from adipic acid) had m. p. 239—241°, undepressed on admixture with an authentic specimen of m. p. 240—242°. The solid (100 μg.) from a 5 μl. aliquot part of an acetone solution, counted as indicated, gave 3050 c.p.m. (sp. activity 0·34 mc/g.). Successive recrystallisations from acetone–methanol did not change the specific activity, and radiochemical purity was further demonstrated by reversed-phase paper chromatography with the authentic compound as carrier; soya-bean oil [13] or Vaseline (1—3% v/v in ether) was used as stationary phase and acetone–water (4 : 1) or ethanol–water (9 : 1) as mobile solvent.

[^{14}C]*Endrin*.—36% Peracetic acid (0·125 g.) was added dropwise to [^{14}C-isodrin] (0·1 g.) in benzene (0·5 c.c.). After being shaken at room temperature for 19 hr., then at 45° for 1 hr., the mixture was diluted with an equal volume of water, and the benzene expelled at 110°. The solid was filtered off from the cooled mixture, washed with water, and recrystallised from methanol, to give endrin (0·0528 g.), m. p. 243—245° (decomp.), undepressed on admixture with an authentic specimen, m. p. 244—245° (decomp.). A second crop (0·0378 g.) had the same m. p. and specific activity (0·33 mc/g.).

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Department of Scientific and Industrial Research,
Pest Infestation Laboratory, London Road
Slough, Bucks.

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740. *The Preparation and Structure of Halogen-bridged Anionic Complexes of Bivalent Palladium and Platinum.*

By C. M. Harris, S. E. Livingstone, and N. C. Stephenson.

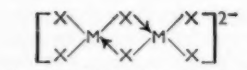
The halogen-bridged ions $[Pd_2X_6]^{2-}$ (X = Cl, Br, I) and $[Pt_2X_6]^{2-}$ (X = Br, I) have been isolated from solutions of corresponding tetrahalogeno-ions $[MX_4]^{2-}$ (M = Pd, Pt) as their quaternary ammonium or arsonium salts. *X*-Ray crystal analysis of the compound $[NEt_4]_2[Pt_2Br_6]$ has confirmed the existence of a discrete planar bromo-bridged anion $[Pt_2Br_6]^{2-}$. Cryoscopic ionic-weight measurements on $[NEt_4]_2[Pd_2Br_6]$ and $[AsPh_3Me]_2[Pd_2Cl_6]$ in nitrobenzene, and ebullioscopic measurements on the former in acetone, confirm the existence of the dimeric anions in solution.

Numerous compounds containing $[MX]_4^{2-}$ ions (M = Pd, Pt; X = Cl, Br, I) have been reported.[1] Potassium chloropalladate(II) and chloroplatinate(II) have been shown to be isomorphous and to possess a square planar configuration of chlorine atoms about the metal atom.[2] Gutbier and Fellner,[3] as long ago as 1916, isolated a series of complex palladium(II) chlorides and bromides of organic bases, [BH][PdX_3] (B = tri-*n*-propylamine, tri*iso*butylamine, guanidine, etc.; X = Cl, Br). Nothing has been reported about the structure of these compounds and they have been classed by Sidgwick [4] as examples

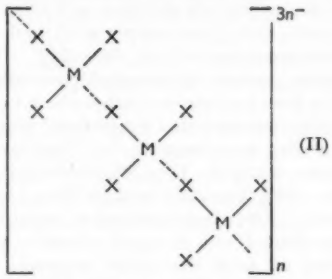
[1] Sidgwick, "The Chemical Elements and their Compounds," Clarendon Press, Oxford, 1950, pp. 1508, 1605.
[2] Dickinson, *J. Amer. Chem. Soc.*, 1922, **44**, 2404.
[3] Gutbier and Fellner, *Z. anorg. Chem.*, 1916, **95**, 169.
[4] Sidgwick, *op. cit.*, p. 1561.

XUM

of three-covalent palladium. Sundaram and Sandell [5] have recently examined spectrophotometrically the chloro-complexes of palladium present in solutions of palladium(II) perchlorate in M-perchloric acid, containing varying amounts of chloride. They have identified species containing palladium and chlorine atoms in the ratios 1 : 1; 1 : 2; 1 : 3;



(I) (M = Pd, Pt; X = Cl, Br, I)



(II)

1 : 4. The dissociation constants of the alleged species, $[PdCl]^+$, $PdCl_2$, $[PdCl_3]^-$, and $[PdCl_4]^{2-}$, have been recently determined [6] in dilute perchloric acid solution. Sundaram and Sandell observed a lowering of the extinction coefficient of the $[PdCl_4]^{2-}$ ion in perchloric acid on the addition of excess of chloride. Although they postulated the existence of higher complexes, $[PdCl_5]^{3-}$ and $[PdCl_6]^{4-}$, they did not succeed in establishing the composition of these higher complexes. Harris, Livingstone, and Reece [7] recently proved spectrophotometrically the existence of $[PdBr_6]^{4-}$ ions in nitrobenzene solutions of $[PdBr_4]^{2-}$ ions in the presence of an excess of bromide ions. The existence of other ionic species is possible but only one was identified.

The $[PdCl_3]^-$ ion, reported by Sundaram and Sandell to occur in solution, was earlier suggested by Gutbier and Fellner [3] as present in the chloro-compounds prepared by them. Although a tetragonal-distorted octahedral arrangement for palladium(II) has been described,[8] there are no cases in which the palladium(II) atom has been shown to have a co-ordination number less than four. Consequently, we investigated complexes containing the alleged $[PdX_3]^-$ ion and attempted to prepare the corresponding platinum compounds. If these compounds should be four-covalent there are at least two possibilities: a discrete dimeric halogen-bridged anion (I), and a polymeric chain-ion structure (II). The compound $CsCuCl_3$ has been shown by Wells [9] to contain structure (II), where the chains are arranged so as to give the copper atoms a distorted octahedral arrangement.

We have isolated the following new compounds: NMe_4PtI_3; NEt_4MX_3, where M = Pd, X = I, and M = Pt, X = Br, I; $NPhMe_3MI_3$, where M = Pd, Pt; $AsPh_3MePdCl_3$. The chloro- and the bromo-complexes were obtained by metathesis from aqueous solution of $[MX_4]^{2-}$ ions and the substituted ammonium or arsonium halide. The iodo-compounds were prepared by treating aqueous-alcoholic solutions of palladium(II) or platinum(II) iodide containing excess of sodium iodide with the appropriate substituted ammonium iodide.

A two dimensional *X*-ray structural determination has been carried out on a single crystal of the tetraethylammonium compound, NEt_4PtBr_3. The results show that there is no discrete $[PtBr_3]^-$ group in the solid state but the binuclear halogen-bridged anion, $[Pt_2Br_6]^{2-}$, with the dimensions listed on p. 3702. Within experimental error a distinction between a slightly distorted bridge and a completely symmetrical one is not possible. The average Pt–Br bond distances are $2{\cdot}43 \pm 0{\cdot}05$ Å. A refinement using three-dimensional data is in progress to ascertain any small real difference between terminal and

[5] Sundaram and Sandell, *J. Amer. Chem. Soc.*, 1955, **77**, 855.
[6] Droll, Block, and Fernelius, Pennsylvania State Univ., 1956, Contract No. AT(3)—1—907.
[7] Harris, Livingstone, and Reece, *Austral. J. Chem.*, 1957, **10**, 282.
[8] Harris, Nyholm, and Stephenson, *Nature*, 1956, **177**, 1127.
[9] Wells, *J.*, 1947, 1662.

bridged bond lengths. The average Pt–Br bond distance, 2·43 Å, for all Pt–Br bonds in the molecule agrees, within experimental error, with the sum of the covalent radii (1·31 + 1·14 = 2·45 Å) of these elements.[10] This result is similar to that of Mann and Wells [11] for the bromo-bridged complex of palladium with trimethylarsine, $[Me_3AsPdBr_2]_2$. In this compound all the Pd–Br bond lengths were equivalent at 2·45 Å.

TABLE 1. *Molecular conductivities in nitrobenzene.*

Compound	Colour	Mol. conductance of 10^{-3}M-solutions at 25° (mho cm.$^{-2}$)
$[AsPh_3Me]_2[Pd_2Cl_6]$	Brownish-pink	53·7
$[NEt_4]_2[Pd_2Br_6]$	Brown	60·5
$[NEt_4]_2[Pd_2I_6]$	Black	60·6
$[NPhMe_3]_2[Pd_2I_6]$	Black	60·6
$[NEt_4]_2[Pt_2Br_6]$	Yellowish-brown	55·0
$[NMe_4]_2[Pt_2I_6]$	Yellowish-brown	63·5
$[NPhMe_3]_2[Pt_2I_6]$	Yellowish-brown	56·7
$[NEt_4]_2[Pt_2I_6]$	Yellowish-brown	58·6
$[AsPh_3Me]_2[PdCl_4]$	Pink	51·0
$[NEt_4]_2[PdBr_4]$	Pinkish-brown	60·5
$[AsPh_3Me]_2[PtCl_4]$	Pale pink	Insol.

Single crystals of the analogous palladium compound, which were suitable for the measurement of cell dimensions, could not be obtained. However, the powder photograph of this compound is similar to that of the platinum compound. It is reasonable to assume that all these compounds contain the $[M_2X_6]^{2-}$ anion.

Although many binuclear neutral complexes of bivalent palladium and platinum [12,13] and a cationic bridged complex of platinum(II) [13] have been reported, we know of no palladium or platinum complexes which have been previously shown to contain halogen-bridged anions. The compounds which were prepared in this investigation are listed in Table 1, along with their molecular conductivities in nitrobenzene. The iodo-compounds are interesting since few iodo-bridged complexes of these metals have been reported.[14]

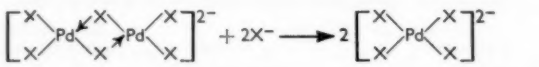
The conductivities of these compounds containing the $[M_2X_6]^{2-}$ ion are comparable with those of di-univalent electrolytes in nitrobenzene. Some tetrahalogeno-complexes with the cations, $[AsPh_3Me]^+$ and $[NEt_4]^+$, were prepared for comparison; they are listed at the bottom of Table 1. The conductivities of these compounds are similar to those of the complexes containing the $[M_2X_6]^{2-}$ ion. We were unable to isolate pure triphenylmethylarsonium tetrachloro-$\mu\mu'$-dichloroplatinate(II), the compound being contaminated with the tetrachloroplatinate(II) derivative: since both products are insoluble, it was not possible to separate them.

Ionic-weight measurements were made (see Table 2) on the chloro- and the bromo-bridged compounds, $[AsPh_3Me]_2[Pd_2Cl_6]$ and $[NEt_4]_2[Pd_2Br_6]$, in order to determine whether the dimeric anions persist as such in solution. The determinations by Foss and Gibson [15] for a uni-bivalent gold complex, [Au dipy $Et_2]_2[Au_2Et_4(SO_4)_2]$ (dipy = 2 : 2′-dipyridyl), over a comparable concentration range are given for comparison. The mean van't Hoff factors obtained for $[AsPh_3Me]_2[Pd_2Cl_6]$ and $[NEt_4]_2[Pd_2Br_6]$ are comparable with those obtained for $[NEt_4]_2[PdBr_4]$ and Foss and Gibson's gold complex, indicating that the bridged ion is present in solution. If it were assumed that the compounds form a solvated $[MX_3]^-$ ion in solution, the van't Hoff factors, calculated on the monomeric formulæ, would be in the range 1·0—1·1. Measurements by Foss and Gibson [15] on some

[10] Pauling, "The Nature of the Chemical Bond," Cornell Univ. Press, 2nd edn., 1945, p. 179.
[11] Mann and Wells, *J.*, 1938, 702.
[12] Jensen, *Z. anorg. Chem.*, 1935, **225**, 97; Mann, *Ann. Reports*, 1938, **35**, 148; Chatt and Mann, *J.*, 1939, 1622; Chatt, *J.*, 1950, 2301; 1951, 652; Chatt and Hart, *J.*, 1953, 2363; Livingstone and Plowman, *J. Proc. Roy. Soc. New South Wales*, 1950, **84**, 188; 1951, **85**, 116; Livingstone, *J.*, 1956, 1988.
[13] *Idem*, *ibid.*, p. 1994.
[14] Cf., however, Mann and Purdie, *J.*, 1938, 883.
[15] Foss and Gibson, *J.*, 1949, 3063.

uni-univalent electrolytes in this concentration range give van't Hoff factors of the order of 1·8.

Treatment of $[AsPh_3Me]_2[Pd_2Cl_6]$ and $[NEt_4]_2[Pd_2Br_6]$ in acetone solution with triphenylmethylarsonium chloride and tetraethylammonium bromide, respectively, gives precipitates of the tetrahalogeno-compounds, $[AsPh_3Me]_2[PdCl_4]$ and $[NEt_4]_2[PdBr_4]$. This reaction involves the splitting of the dimeric bridged anions as shown thus:



Attempts were made to convert the bridged platinum complex, $[NEt_4]_2[Pt_2Br_6]$, into the tetrabromo-compound, $[NEt_4]_2[PtBr_4]$, in acetone, but only the original compound was recovered.

It is interesting that most of the bridged compounds were prepared from aqueous solution; this suggests that the bridged ion, $[M_2X_6]^{2-}$, is not decomposed by water.

TABLE 2. *Ionic-weight determinations.*

Compound	Method	Concn. range (%)	Mean obs. ionic wt.	*M* (theor.)	van't Hoff factor *M* (theor.) / Mean obs. ionic wt.
$[AsPh_3Me]_2[Pd_2Cl_6]$	Cryoscop. in $PhNO_2$	0·13—0·69	490	1069	2·2
$[NEt_4]_2[Pd_2Br_6]$	Cryoscop. in $PhNO_2$	0·17—0·69	465	953	2·0
,, ...	Ebullioscop. in $COMe_2$	0·69—2·31	425	953	2·2
$[NEt_4]_2[PdBr_4]$	Cryoscop. in $PhNO_2$	0·26	295	686	2·3
[Au dipy Et_2]$_2$[$Au_2Et_4(SO_4)_2$]	Cryoscop. in $PhNO_2$	0·6—1·8	758	1524	2·0

EXPERIMENTAL

Triphenylmethylarsonium Tetrachloro-μμ'-dichlorodipalladate(II).—An aqueous solution of potassium tetrachloropalladate(II) (1·28 g.) was added to a solution of triphenylmethylarsonium chloride (2·84 g.) in water (20 ml.). The resulting pink precipitate was filtered off, washed with water, and recrystallised from 80% aqueous acetone (150 ml.) to give brownish-pink crystals of the pure *compound* (Found: C, 42·9; H, 3·4; Cl, 19·8; Pd, 20·0%; *M*, cryoscop. in $PhNO_2$: 0·13% solution, 440; 0·20%, 450; 0·30%, 480; 0·39%, 500; 0·55%, 550; 0·69%, 520 $C_{38}H_{36}As_2Cl_6Pd_2$ requires C, 42·7; H, 3·4; Cl, 19·9; Pd, 20·0%; *M*, 1069).

Tetraethylammonium Tetrabromo-μμ'-dibromodipalladate(II).—Potassium tetrabromopalladate(II) (3·0 g.) dissolved in water (50 ml.) was added to an aqueous solution of tetraethylammonium bromide (1·6 g.). The resulting precipitate was filtered off and recrystallised from 1 : 1 acetone–alcohol (100 ml.) as brown plates (1·8 g.) (Found: C, 20·4; H, 4·4; N, 2·7; Br, 49·5; Pd, 22·4%; *M*, cryoscop. in $PhNO_2$: 0·17% solution, 470; 0·39%, 470; 0·69%, 455; *M*, ebullioscop. in $COMe_2$: 0·69%, 380; 0·86%, 440; 1·35%, 380; 1·71%, 450; 2·31%, 470. Calc. for $C_{16}H_{40}N_2Br_6Pd_2$: C, 20·2; H, 4·2; N, 2·9; Br, 50·2; Pd, 22·4%; *M*, 953).

Tetraethylammonium Tetraiodo-μμ'-di-iododipalladate(II).—Palladium(II) iodide (0·40 g.) was dissolved in boiling ethanol (30 ml.) containing sodium iodide (1·5 g.). The filtered solution was added to tetraethylammonium iodide (0·7 g.) in boiling 90% ethanol (10 ml.). There was an immediate precipitate of black crystals of the *compound* which, after a few minutes, was filtered off, and washed with ethanol, followed by ether (yield, 0·64 g.) (Found: C, 15·6; H, 3·4; N, 2·4; Pd, 17·4. $C_{16}H_{40}N_2I_6Pd_2$ requires C, 15·6; H, 3·3; N, 2·3; Pd, 17·3%).

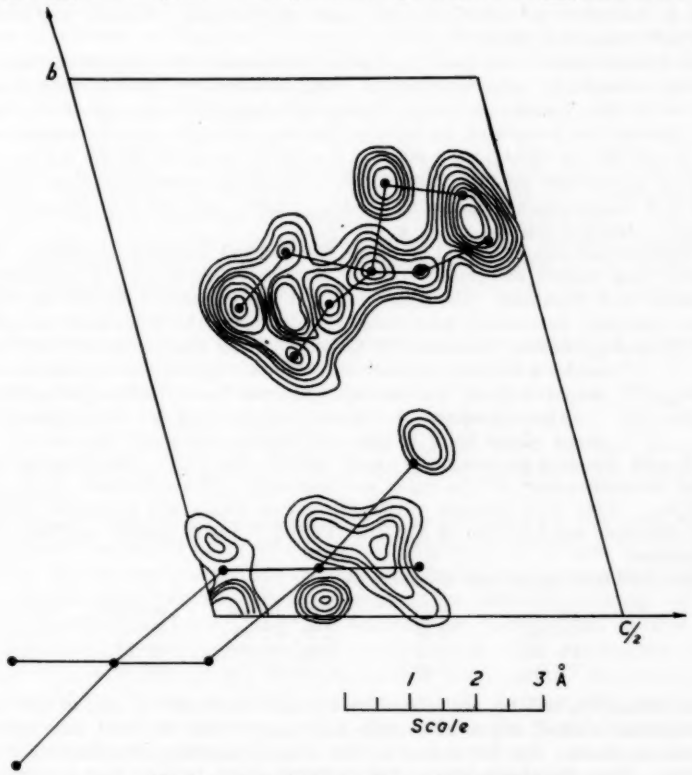
Trimethylphenylammonium Tetraiodo-μμ'-di-iododipalladate(II).—Palladium(II) iodide (1 g.) and sodium iodide (3 g.) were dissolved in hot ethanol (60 ml.) and treated with trimethylphenylammonium iodide (1·45 g.) in 90% ethanol (30 ml.). Crystals began to be deposited from the warm solution. The mixture was placed on the steam-bath for 30 min., cooled, and filtered, and the black crystals (1·35 g.) of the *compound* washed with a little alcohol (Found: N, 2·2; Pd, 17·1. $C_{18}H_{22}N_2I_6Pd_2$ requires N, 2·2; Pd, 17·1%).

Tetraethylammonium Tetrabromo-μμ'-dibromodiplatinate(II).—Potassium tetrachloroplatinate(II) (1 g.) was dissolved in water (20 ml.) containing sodium bromide (1 g.). This solution was

added to tetraethylammonium bromide (1 g.) in water (8 ml.). After 3 hr. on the steam-bath, the mixture was filtered and the product (0·84 g.) washed with a little cold water and recrystallised from acetone (50 ml.), to give yellowish-brown plates (0·52 g.) of the *complex* (Found: C, 17·5; H, 3·5; N, 2·5; Br, 41·5; Pt, 35·2. $C_{16}H_{40}N_2Br_6Pt_2$ requires C, 17·0; H, 3·6; N, 2·5; Br, 42·4; Pt, 34·6%). Single crystals for *X*-ray examination were obtained by allowing a nitrobenzene solution to evaporate in air (Found: Pt, 35·1%).

Tetraethylammonium Tetraiodo-μμ′-di-iododiplatinate(II).—Platinum(II) iodide (0·5 g.) was dissolved in a boiling aqueous solution (25 ml.) of potassium iodide (5 g.). The filtered solution was added to tetraethylammonium iodide (1 g.) in water (15 ml.) at the b. p. Buff crystals of

First ($F_{obs.}$–$F_{calc.}$) *Fourier synthesis showing resolution of* NEt_4^+ *ion.* $F_{calc.}$ *from* Pt *and* Br *alone.*



(Contours = 1 eÅ^{-2}; *negative regions omitted.*)

the *compound* were immediately precipitated; the product was filtered off and washed with water, followed by ethanol and ether (yield, 0·6 g.) (Found: C, 13·4; H, 2·9; N, 1·8; Pt, 27·9. $C_{16}H_{40}N_2I_6Pt_2$ requires C, 13·6; H, 2·9; N, 2·0; Pt, 27·9%).

Trimethylphenylammonium Tetraiodo-μμ′-di-iododiplatinate(II).—Prepared as for the analogous tetraethylammonium compound by using trimethylphenylammonium iodide (1 g.) (yield 0·8 g.), the *compound* was recrystallised from ethanol (600 ml.) (Found: C, 15·2; H, 2·1; N, 1·8; Pt, 27·4. $C_{18}H_{28}N_2I_6Pt_2$ requires C, 15·2; H, 2·0; N, 2·0; Pt, 27·4%).

Tetramethylammonium Tetraiodo-μμ′-di-iododiplatinate(II).—The yellowish-brown *compound* was prepared as for the analogous tetraethylammonium complex by using tetramethylammonium iodide (1 g.) (yield 0·3 g.) (Found: Pt, 30·0. $C_8H_{24}N_2I_6Pt_2$ requires Pt, 30·0%).

XUM

Triphenylmethylarsonium Tetrachloropalladate(II).—Triphenylmethylarsonium tetrachloro-μμ′-dichlorodipalladate(II) (0·52 g.), dissolved in hot acetone (200 ml.), was added to triphenylmethylarsonium chloride (2 g.) in boiling acetone (200 ml.) containing a few ml. of water. Pink crystals of the *complex* (0·84 g.) were slowly deposited (Found: C, 50·0; H, 4·2; Cl, 15·9; Pd, 12·0. $C_{38}H_{36}Cl_4As_2Pd$ requires C, 51·2; H, 4·1; Cl, 15·9; Pd, 12·0%).

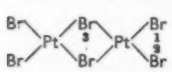
Tetraethylammonium Tetrabromopalladate(II).—This compound was prepared as described by Harris, Livingstone, and Reece [7] (Found: C, 27·8; H, 6·2; N, 3·9; Br, 46·5; Pd, 15·5. Calc. for $C_{16}H_{40}N_2Br_4Pd$: C, 28·0; H, 5·9; N, 4·1; Br, 46·5; Pd, 15·5%).

Triphenylmethylarsonium Tetrachloroplatinate(II).—A solution of potassium chloroplatinate(II) (0·42 g.) in 2M-hydrochloric acid (30 ml.) was treated at the b. p. with an aqueous solution (20 ml.) of triphenylmethylarsonium chloride (0·75 g.). A pale pink precipitate was filtered off, washed with boiling 2N-hydrochloric acid, then acetone, and dried (yield, 0·9 g.). The *compound* is insoluble in water, acetone, and nitrobenzene (Found: C, 46·6; H, 3·6. $C_{38}H_{36}Cl_4As_2Pt$ requires C, 46·6; H, 3·7%).

Crystallographic Data.—A single crystal of tetraethylammonium tetrabromo-μμ′-dibromodiplatinate(II), obtained by slow evaporation from nitrobenzene, was investigated by *X*-ray diffraction methods. Buerger precession photographs, taken with the use of Mo characteristic radiation, showed the compound to have a triclinic unit cell with dimensions as follows: $a = 7{\cdot}60$, $b = 8{\cdot}38$, $c = 12{\cdot}34$ Å, $\alpha = 105°\,35'$, $\beta = 84°\,0'$, $\gamma = 112°\,50'$ (all $\pm\frac{1}{2}\%$).

The structure analysis has proceeded satisfactorily on the assumption that the space group is $P\bar{1}$ and that the crystal has one unit of $[NEt_4]_2[Pt_2Br_6]$ per unit cell (calculated density = 2·66 g. cm.$^{-3}$; observed density = 2·60 g. cm.$^{-3}$).

The Patterson function, projected on planes 010 and 100, has been calculated. The centric Pt–Pt vector was readily recognised, and by suitable origin shifts the co-ordinates of the bromine atoms were obtained. The signs of all but the weakest of the *h*0*l* and 0*kl* structure factors were uniquely determined from these co-ordinates. The refinement has proceeded by successive (F_{obs}–F_{calc}) Fourier synthesis (cf. Figure). Using Hartree atomic scattering factors and an isotropic temperature factor, determined by statistical methods, we have found the reliability indexes to be $R(h0l) = 0{\cdot}14$, $R(0kl) = 0{\cdot}13$.



The refinement of the structure has not yet been carried beyond the stage where bond lengths and angles involving the heavier atoms are established with standard deviations of about 0·03 Å and 2·5°. The following points concerning the stereochemistry of the anion are, however, well established: in the compound, $[NEt_4]_2[Pt_2Br_6]$, there exist discrete $[Pt_2Br_6]^{2-}$ anions which are separated from adjacent anions by distances not less than 6 Å. The $[Pt_2Br_6]^{2-}$ ion is planar and with a configuration as annexed.

The calculated bond angles and distances (Å) are:

$Pt–Br_1$	2·40	$\angle Br_3–Pt–Br_1$	87° 15′
$Pt–Br_2$	2·41	$\angle Br_1–Pt–Br_2$	95° 13′
$Pt–Br_3$	2·53	$\angle Br_2–Pt–Br_4$	87° 32′
$Pt–Br_4$	2·38	$\angle Br_4–Pt–Br_3$	90° 00′

Bromine atoms Br_3 and Br_4 are related by a centre of symmetry, and in the 0*kl* electron-density projection a small degree of overlap lends uncertainty to the *y*-parameters of these bridged bromine atoms. For this reason further three-dimensional refinement of the structure is in progress. From the above information, however, it can be seen, that the bridge deviates little, if any, from a regular square, and, within the present limits of experimental error, the terminal and bridged Pt–Br bond distances have a mean of 2·43 ± 0·05 Å.

The authors are indebted to Dr. E. Challen, of the microanalytical laboratory of this University, for the analyses of carbon, hydrogen, and nitrogen.

Department of Inorganic Chemistry, New South Wales University of Technology, Sydney, Australia. [*Received, May 8th*, 1958.]

741. *The Preparation of the Five 2-Methyl-x-phenylpentanes.*

By G. M. K. Hughes.

The five 2-methyl-*x*-phenylpentanes have been prepared, all but 4-methyl-1-phenylpentane by new routes. Reduction of 2-methyl-1-phenylpent-1-en-3-one gave 2-methyl-1-phenylpentane, and of 4-methyl-4-phenylpentan-2-one gave 2-methyl-2-phenylpentane. 2-Methyl-3- and -4-phenylpentane have been obtained by use of phosphorylenes (Wittig–Schöllkopf reaction). 2-Methyl-4-phenylpentane has been synthesised by hydrogenolysis of 4-methyl-2-phenylpentan-2-ol.

The five 2-methyl-*x*-phenylpentanes were required as reference compounds in a study of the alkylation of benzene by the 2-methylpent-*x*-enes, and as models for the unambiguous synthesis of more complex alkylbenzenes. Hence a number of alternative synthetic methods have been examined, and gas-liquid chromatography has been employed to establish purity and identity. Methods involving alkylation were avoided.

2-Methyl-1-phenylpentane has been prepared previously by (*a*) reduction of the unsaturated alcohol obtained from phenylmagnesion bromide and 2-methylpent-2-enal,[1] and (*b*) by two-stage reduction of α-methylvalerophenone.[2] It also arises as a minor product in the sodamide cleavage of α-benzyl-α-methylvalerophenone.[3] The hydrocarbon has now been obtained by a simple two-stage reduction of 2-methyl-1-phenylpent-1-en-3-one (1-benzylidenediethyl ketone); this is readily available by an acid-catalysed condensation; dilute aqueous alkali as catalyst yields the corresponding β-hydroxy-ketone in low yield.

Reported syntheses of 2-methyl-2-phenylpentane are (*a*) by alkylation of benzene by 2-chloro-2-methylpentane,[4] (*b*) by reduction of the product from alkylation of benzene with 4-chloro-4-methylpent-1-ene,[5] and (*c*) by reaction of the Grignard reagent from 2-methyl-2-phenylpropyl chloride with ethyl toluene-*p*-sulphonate.[6] Repetition of method (*c*) gave a 14% yield of the alkylbenzene but the latter is much more readily available by Wolff–Kishner reduction of 4-methyl-4-phenylpentan-2-one (from mesityl oxide and benzene).

2-Methyl-3- and 2-methyl-4-phenylpentane can be obtained by the same methods, the most frequently employed being that generally attributed to Klages.[7] This consists in dehydrating the appropriate tertiary alcohol and reducing the resultant olefin. In addition 2-methyl-3-phenylpentane has been prepared by sodamide cleavage of 2 : 2-dimethyl-1 : 3-diphenylpentan-1-one,[8] and the 4-isomer by dehydration of the tertiary alcohol obtained from phenylmagnesium and mesityl oxide, with subsequent reduction of the diene.[9] Klages's method has been repeated in both cases. The recent work of Wittig and Schöllkopf[10] has provided another method of generating hydrocarbons unambiguously, and this has been applied in this series. Ethylenetriphenylphosphine on reaction with *iso*butyrophenone gave a 1 : 1 mixture of *cis*- and *trans*-4-methyl-3-phenylpent-2-ene in 90% yield, while a 58% yield of 4-methyl-2-phenylpent-1-ene was obtained from methylenetriphenylphosphine and *iso*valerophenone. Reduction of the olefins afforded the required alkylbenzenes. A further variant of Klages's method consists

[1] Bjeluoss, *Ber.*, 1912, **45**, 625.
[2] Stenzl and Fichter, *Helv. Chim. Acta*, 1937, **20**, 846.
[3] Dumesnil, *Ann. Chim.* (*France*), 1917, **8**, 70.
[4] Schreiner, *J. prakt. Chem.*, 1910, **82**, 292.
[5] Cologne and Garnier, *Bull. Soc. chim. France*, 1948, **15**, 436.
[6] Pines, Huntsman, and Ipatieff, *J. Amer. Chem. Soc.*, 1953, **75**, 2311.
[7] Klages, *Ber.*, 1904, **37**, 1721, 2301; Huston, Guile, Bailey, Curtis, and Esterdahl, *J. Amer. Chem. Soc.*, 1945, **67**, 899; Huston and Kaye, *ibid.*, 1942, **64**, 1576.
[8] Albesco, *Ann. Chim.* (*France*), 1922, **18**, 216.
[9] Levina, Tantsyreva, Fainzilberg, and Mezentsova, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 1951, 161; *Chem. Abs.*, 1951, **45**, 9456.
[10] Wittig and Schöllkopf, *Ber.*, 1954, **87**, 1318.

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in cleavage by sodium and ethanol in liquid ammonia of the tertiary benzylic alcohols:[11] applied to 4-methyl-2-phenylpentan-2-ol it constituted the easiest synthesis of unlimited quantities of 2-methyl-4-phenylpentane. However, only partial reduction of 2-methyl-3-phenylpentan-3-ol was achieved, and it was not possible to separate the alcohol from the hydrocarbon by distillation over sodium. The use of lithium–ethanol in both ammonia and diethylamine again only effected partial reduction. Since steric factors are unlikely to account for the difference in the behaviour of the alcohols, no explanation or rationalisation is offered.

The last alkylbenzene, 4-methyl-1-phenylpentane, has been made previously by Wurtz–Fittig reactions[12] and by reduction of γ-methylvalerophenone.[13] The last method has been repeated.

In general reference has not been made to alkylations which have yielded these alkylbenzenes, even though the reported physical constants are often in good agreement with those recorded here. Reference is made only to other formal synthetic studies, despite poorer agreement. Attention is drawn to Francis's comments[14] on the limited value of constants as a guide to purity and identity in this field.

Experimental

Infrared absorptions were measured on a G.S.2 Grubb-Parsons spectrometer. Gas–liquid chromatograms were effected on Apiezon L supported on C-22 firebrick at 213°. M. p.s were taken on a Kofler block and are uncorrected.

2-Methyl-1-phenylpent-1-en-3-one.—Diethyl ketone (22·8 g.), benzaldehyde (28·0 g.), and 10N-hydrochloric acid (55 ml.) were heated under reflux for 4 hr. (cf. ref. 15). The cooled mixture was extracted with ether, and the combined extracts were washed with water, sodium hydrogen carbonate solution, and water. The dried ($MgSO_4$) extract was evaporated, and the residue distilled to give the unsaturated ketone, b. p. 122—124°/5 mm. (lit.,[16] 163°/20 mm.), which crystallised (21·8 g., 53%); $\nu_{max.}$ 1661 (CO·C=C), 1623 (Ph·C=C), and 802 (CR_2=CHR) cm.$^{-1}$. The 2 : 4-*dinitrophenylhydrazone*, red prisms from ethanol–chloroform, had m. p. 181—183° (Found: C, 61·1; H, 4·7; N, 16·1. $C_{18}H_{18}O_4N_4$ requires C, 60·9; H, 5·1; N, 15·8%). The semicarbazone, from benzene, had m. p. 183° (lit.,[16] 188°) (Found: C, 67·3; H, 7·5; N, 18·1. Calc. for $C_{13}H_{17}ON_3$: C, 67·4; H, 7·3; N, 18·2%).

The same product was obtained in 9% overall yield by dehydrating (toluene-*p*-sulphonic acid) 1-*hydroxy*-2-*methyl*-1-*phenylpentan*-3-*one*, b. p. 131—137°/3 mm., which was formed by stirring together for 3 days benzaldehyde (42·0 g.), diethyl ketone (118·5 ml.), water (40 ml.), ethanol (95 ml.), and 10% sodium hydroxide solution (10 ml.).

2-Methyl-1-phenylpentan-3-one.—2-Methyl-1-phenylpent-1-en-3-one (18·2 g.) was hydrogenated in ethanol in the presence of 10% palladium–carbon until 1 mol. of hydrogen had been absorbed. The *ketone* had b. p. 244—251°, n_D^{20} 1·5037 (15·5 g., 84%), $\nu_{max.}$ 1706 (sat. C=O), 742 (Ph), and 700 (Ph) cm.$^{-1}$ (Found: C, 81·5; H, 9·3. $C_{12}H_{16}O$ requires C, 81·7; H, 9·1%). The 2 : 4-*dinitrophenylhydrazone*, yellow rhombs from ethanol–chloroform, had m. p. 159° (Found: C, 60·7; H, 5·7; N, 15·9. $C_{18}H_{20}O_4N_4$ requires C, 60·7; H, 5·6; N, 15·7%). The *semicarbazone*, needles from benzene–light petroleum (b. p. 40—60°), had m. p. 116—117° (Found: C, 66·4; H, 7·9; N, 17·9. $C_{13}H_{19}ON_3$ requires C, 66·8; H, 8·1; N, 18·0%).

2-Methyl-1-phenylpentane.—2-Methyl-1-phenylpentan-3-one (11·5 g.), potassium hydroxide pellets (12·4 g.), and 80% hydrazine hydrate (8·8 ml.) yielded, by the Huang-Minlon modification[17] of the Wolff–Kishner reduction, the alkylbenzene, b. p. 210—218° (6·23 g., 59%). Redistillation over sodium gave an analytical specimen, b. p. 216—218°, n_D^{20} 1·4880 (lit., 214°/740 mm.[3]; n_D^{25} 1·4827 [1]) (Found: C, 89·1; H, 11·0. Calc. for $C_{12}H_{18}$: C, 89·9; H, 11·1%).

2-Methyl-2-phenylpentane.—(*a*) 4-Methyl-4-phenylpentane-2-one, prepared in 86% yield from benzene and mesityl oxide, had b. p. 145°/37 mm. (lit.,[18] 134°/22 mm.), $\nu_{max.}$ 1704 (sat. C=O),

[11] Birch, *J.*, 1945, 809.
[12] Schramm, *Annalen*, 1883, **218**, 383; Stenzl and Fichter, *Helv. Chim. Acta*, 1934, **17**, 669.
[13] Berliner and Berliner, *J. Amer. Chem. Soc.*, 1950, **72**, 222.
[14] Francis, *Chem. Rev.*, 1948, **42**, 107.
[15] Metayer and Epinay, *Compt. rend.*, 1948, **226**, 1095.
[16] Vorlander, *Annalen*, 1896, **294**, 253.
[17] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.
[18] Hoffman, *ibid.*, 1929, **51**, 2542.

1030 (vs), 763 (Ph), and 697 (Ph) cm.$^{-1}$. Wolff–Kishner reduction as above gave, after redistillation over sodium, the alkylbenzene (70%), b. p. 206—208°, n_D^{20} 1·4935. Homogeneity and identity were established by comparison of the infrared spectrum with that of the specimen prepared as below, and by gas–liquid chromatography.

(*b*) Preparation of the alkylbenzene by the method of Pines *et al.*[6] from the Grignard reagent of 2-methyl-2-phenylpropyl chloride (b. p. 112—114°/21 mm., n_D^{20} 1·5232) and ethyl toluene-*p*-sulphonate gave the hydrocarbon (14% yield), b. p. (from sodium) 196—197°, n_D^{20} 1·4943 (lit.,[4-6] 126·8—127°/66 mm., 205—206°; n_D^{20} 1·4929). The infrared absorption was identical with the published curve,[6] and the product was shown to be homogeneous by gas–liquid chromatography.

2-*Methyl*-3-*phenylpentan*-3-*ol.*—*iso*Butyrophenone (b. p. 221—223°, n_D^{20} 1·5175; 2 : 4-dinitrophenylhydrazone, m. p. 161—162°) with ethylmagnesium bromide gave the tertiary alcohol (95%), b. p. 107—109°/11 mm., n_D^{20} 1·5153 (lit.,[19,7] 125—130°/25 mm., 106—112°/8 mm., n_D^{20} 1·5155) (Found: C, 80·9; H, 10·3. Calc. or $C_{12}H_{18}O$: C, 81·0; H, 10·1%).

2-*Methyl*-3-*phenylpentane.*—The above alcohol on dehydration (toluene-*p*-sulphonic acid) yielded the calculated amount of water and gave the corresponding olefin(s) (55% yield), b. p. 201°, n_D^{20} 1·5151 (lit.,[19,20] 206—208°, n_D^{20} 1·5104, $n_D^{18·7}$ 1·5131), $\nu_{max.}$ 1656 (Ar·C=C), 830 (w) (CHR=CR_2) cm.$^{-1}$. Quantitative reduction in ethanol in the presence of platinum gave 2-methyl-3-phenylpentane, b. p. 213°, n_D^{20} 1·4851 (lit.,[6,9] 199—200°, 207—209°, n_D^{20} 1·4890, 1·4912) (Found: C, 88·6, H, 11·0%).

4-*Methyl*-3-*phenylpent*-2-*ene.*—Ethyltriphenylphosphonium bromide (23·2 g.; m. p. 205·5°) was added in small portions to a stirred 1·34N-ethereal solution of *n*-butyl-lithium (50 ml.) under nitrogen. Then the red solution was heated under reflux for 5 hr., and *iso*butyrophenone (11 ml.) in ether (50 ml.) added during 45 min. to the cooled solution. The mixture was next heated under reflux for 4 hr., cooled, and filtered. The residue was washed with ether, and the combined filtrates washed with water, dried ($MgSO_4$), and evaporated. The residual yellow oil was chromatographed on alumina in light petroleum (b. p. 40—60°) to yield the olefins (8·92 g., 90%), b. p. 208—210°, n_D^{20} 1·5080. Gas–liquid chromatography showed that the product was a 1 : 1 mixture of the *cis*- and *trans*-isomers (relative retention volume 1·249 ± 0·006), $\nu_{max.}$ 830 (CHR=CR_2) cm.$^{-1}$ (Found: C, 90·3; H, 10·0. $C_{12}H_{16}$ requires C, 90·0; H, 10·0%). Reduction in the presence of platinum in ethanol gave a quantitative yield of 2-methyl-3-phenylpentane, whose homogeneity and identity were established by infrared absorption and gas–liquid chromatography.

Attempted Hydrogenolysis of 4-*Methyl*-3-*phenylpentan*-3-*ol.*—Under the conditions used successfully for 4-methyl-2-phenylpentan-2-ol (see below), only partial reduction, as shown by infrared absorption and gas–liquid chromatography, was obtained. Neither prolonging the reaction time nor the use of lithium–ethanol, in liquid ammonia or in diethylamine, materially increased the yield. Further it was not possible to separate the tertiary alcohol from the required hydrocarbon by distillation from sodium.

4-*Methyl*-2-*phenylpentan*-2-*ol.*—*iso*Butyl methyl ketone with phenylmagnesium bromide gave the tertiary alcohol (86% yield), b. p. 105—107°/11 mm., n_D^{20} 1·5072 (lit.,[19,21] 125—129°/14 mm., n_D^{16} 1·5157) (Found: C, 81·0; H, 10·2%).

2-*Methyl*-4-*phenylpentane.*—(*a*) Dehydration of the preceding alcohol in the usual manner yielded the calculated amount of water and gave the olefin(s), b. p. 203°, n_D^{20} 1·5151 (lit.,[6,21] 207°, 216—220°, n_D^{19} 1·5231 , n_D^{15} 1·516). Quantitative reduction in ethanol in the presence of platinum gave the required alkylbenzene, b. p. 205—206°, n_D^{20} 1·4850. The homogeneity and identity of the product were established by comparison of the infrared spectrum and gas–liquid chromatographic behaviour with those of the hydrocarbon prepared as below.

(*b*) 4-Methyl-2-phenylpentan-2-ol (35·6 g.) was hydrogenolysed as described by Birch [11] to yield the hydrocarbon (59%), b. p. 205—206°, n_D^{20} 1·4850 (lit.,[7,9] 197—198°/735 mm., n_D^{20} 1·4856, 1·4824) (Found: C, 88·5; H, 11·2%).

4-*Methyl*-2-*phenylpent*-1-*ene.*—Methyltriphenylphosphonium iodide (33·0 g.; m. p. 183°) was added in small portions to a stirred 0·52N-ethereal solution of *n*-butyl-lithium (150 ml.) under nitrogen during ½ hr. *iso*Valerophenone (15 ml.) was added to the red solution and the mixture stirred for 2 hr., then filtered. The residue was washed with ether, and the combined filtrates

[19] Protiva *et al.*, *Chem. Listy.*, 1952, **46**, 47; *Chem. Abs.*, 1952, **46**, 8004; Apolit, *Ann. Chim.* (*France*), 1924, **2**, 71.
[20] Auwers and Eisenlohr, *J. prakt. Chem.*, 1910, **82**, 65.
[21] Bodroux and Taboury, *Bull. Soc. chim. France*, 1909, **5**, 812; *Compt. rend.*, 1909, **148**, 1675.

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were washed with water, dried, and evaporated. The residue was chromatographed on alumina in light petroleum (b. p. 40—60°) to give the *olefin* (7·68 g., 58%), b. p. 209°, n_D^{20} 1·5100, $\nu_{max.}$ 1799, 1625 (ArC=C), 985 ($R_2C{=}CH_2$), 776 (Ph) cm.$^{-1}$. The olefin was shown to be homogeneous by gas–liquid chromatography (Found: C, 90·1; H, 10·0%). Reduction of the olefin in the presence of platinum yielded 2-methyl-4-phenylpentane quantitatively, identity and homogeneity being established by infrared absorption and gas–liquid chromatography.

4-Methyl-1-phenylpentane.—This was prepared in 70% yield by reduction of γ-methylvalerophenone (b. p. 136°/17 mm.) by the Wolff–Kishner method as in previous cases. It had b. p. 99—100°/16 mm., n_D^{20} 1·4860 (lit.,[13] 219°, n_D^{20} 1·4853). The homogeneity of the hydrocarbon was confirmed by gas–liquid chromatography.

Gas–Liquid Chromatography.—The relative retention volumes of the five alkylbenzenes were: 2-methyl-3- and -4-methylpentane (irresolvable) 1·000; 2-methyl-2-phenylpeanent 1·126 ± 0·002; 4-methyl- 1·270 ± 0·006 and 2-methyl-1-phenylpentane 1·222 ± 0·003.

The author is indebted to his colleagues for their critical interest and to other members of this Department for their assistance with the practical work. Mr. C. P. Ogden and his assistants are thanked for carrying out analyses and physical measurements. The Directors of this Company are thanked for their permission to publish this work.

Basic Research Department, Thomas Hedley & Co., Ltd.,
City Road, Newcastle upon Tyne, 1.
[Present address: Chemistry Department,
University of Rochester,
Rochester 20, N.Y., U.S.A.]

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742. *Thermodynamics of Ion Association. Part IV.*[1] *Magnesium and Zinc Sulphates.*

By V. S. K. Nair and G. H. Nancollas.

Thermodynamic equilibrium constants for the association in aqueous solution of magnesium and zinc ions with the sulphate ion have been determined by a precise e.m.f. method at various temperatures between 0° and 45°. ΔG, ΔH, and ΔS for the reaction $M^{2+} + SO_4^{2-} \rightleftharpoons MSO_4$ have been calculated and these are discussed.

In a previous paper[1] the thermodynamic properties for the association between the thallous ion and univalent anions have been determined from solubilities and conductivities. We have now investigated the association between similarly charged ions of higher valency type. Since the bisulphate ion is incompletely dissociated and its dissociation constant is known with considerable certainty over a range of temperature,[2] the bivalent metal sulphates can be studied by using the cell H_2,Pt | MSO_4,HCl | AgCl–Ag. Jones and Monk[3] with a similar cell studied magnesium sulphate and obtained e.m.f.s to within 100 μv at temperatures from 20° to 35°. In order to obtain reliable estimates of the association constants, however, very precise measurements are required since an error of ±100 μv in the e.m.f.'s would produce a variation of 10—20% in the association constants.[3] Measurements have been made on similar cells with the refined apparatus described in part V.[2]

Experimental

" AnalaR " magnesium and zinc sulphates were recrystallised three times from conductivity water and dried at 110°. Small samples in weighing tubes having ground glass caps were rendered anhydrous by heating to constant weight in a muffle furnace at 350° to 420°, then dropped into hydrochloric acid solutions of known molality; the solutions were made up by

[1] Part III, Nair and Nancollas, *J.*, 1957, 318.
[2] Nair and Nancollas, *J.*, in the press.
[3] Jones and Monk, *Trans. Faraday Soc.*, 1952, **48**, 929.

weight with conductivity water. The stock solutions were analysed for sulphate by precipitation as barium sulphate [4] and agreement was within 0·03% of the calculated concentrations. The preparation of hydrochloric acid, standardisation of electrodes, and experimental technique will be described later.[2] Experiments were usually made from 0° to 25° and a new cell filling was used for measurements from 25° to 45°. The e.m.f.s obtained at the same temperature with different fillings never varied by more than 30 μv.

Results and Discussion

The e.m.f. of the cell H_2,Pt | HCl(m_1), MSO_4(m_2) | AgCl–Ag is given by

$$E = E^\circ - k \log a_{H^+} a_{Cl^-}$$

or

$$-\log m_{H^-} = (E - E^\circ)/k + \log m_1 + \log \gamma_{H^+} \gamma_{Cl^-}$$

where m represents molality, γ activity coefficient, and $k = 2{\cdot}3026\,RT/F$. Assuming that the only association taking place is that between the bivalent ions, we find the concentrations of ion species $m_{HSO_4^-} = m_1 - m_{H^+}$, $m_{M^{2+}} = m_{HSO_4^-} + m_{SO_4^{2-}}$, and $m_{MSO_4} = m_2 - m_{M^{2+}}$. The ionic strength, $I = m_1 + 4m_2 - 2m_{HSO_4} - 4m_{MSO_4}$, and the dissociation constant of the bisulphate ion, $k_2 = a_{H^+} a_{SO_4^{2-}}/a_{HSO_4^-}$, has the values obtained previously.[1] The association constant, $K = a_{MSO_4}/a_{M^{2+}} a_{SO_4^{2-}}$, was obtained by successive approximations of I by use of Davies's modified form of the Debye–Hückel equation [5]

$$\log \gamma_z = Az^2[I^{\frac{1}{2}}/(1 + I^{\frac{1}{2}}) - CI] \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

in which $C = 0{\cdot}2$. The results are given in Table 1 together with the mean values of K at each temperature.

Dunsmore and James [6] obtained a value $K = 161$ kg. mole^{-1} for magnesium sulphate at 25° from conductivity measurements. Jones and Monk [3] have recalculated these data allowing for a drift in K with concentration and give $K = 185$ kg. mole^{-1}. Robinson and Stokes [7] have re-analysed Dunsmore and James's results using the Bjerrum critical distance for a 2 : 2 electrolyte, $a_i = 14{\cdot}28$ Å, in the activity-coefficient expression and obtained $K = 201{\cdot}6$ kg. mole^{-1}. Jones and Monk [3] have reported a value of 227 kg. mole^{-1} from e.m.f. measurements: the new value being used for k_2,[2] this is reduced to 212 kg. mole^{-1}. Our value at 25°, 179, is in general agreement with these. At 18°, the interpolated value 155·5 kg. mole^{-1} agrees with that of Davies,[8] 164 kg. mole^{-1}, from conductivity measurements. The conductivity of zinc sulphate solutions has been measured by Owen and Gurry [9] who derived $K = 204$ kg. mole^{-1} at 25°. Robinson and Stokes [7] have recalculated these data by the method outlined for magnesium sulphate and obtained $K = 227$ kg. mole^{-1}. At 0° the cryoscopic measurements of Brown and Prue [10] give $K = 111$ kg. mole^{-1} for both magnesium sulphate and zinc sulphate which may be compared with the present values of 92 and 121 kg. mole^{-1} respectively.

The heats of formation, ΔH, have been obtained from the linear plots shown in the Figure of log K against T^{-1} with use of least squares (Table 2).

Davies's expression for activity coefficients with $C = 0{\cdot}2$ in eqn. (1) corresponds to a distance of closest approach of the ions, q, of about 4·3 Å. There is a considerable latitude in the choice of values for this parameter and the subject has received much attention.[10,11,12] Beevers and Lipson's [13] X-ray data for copper sulphate were used by

[4] Vogel, "A Text Book of Quantitative Analysis," Longmans, London, 1947.
[5] Davies, *J.*, 1938, 2093.
[6] Dunsmore and James, *J.*, 1951, 2925.
[7] Robinson and Stokes, "Electrolyte Solutions," Butterworths, London, 1955.
[8] Davies, *Trans. Faraday Soc.*, 1927, **23**, 351.
[9] Owen and Gurry, *J. Amer. Chem. Soc.*, 1938, **60**, 3074.
[10] Brown and Prue, *Proc. Roy. Soc.*, 1955, *A*, **232**, 320.
[11] Guggenheim, *Discuss. Faraday Soc.*, 1957, No. 24, 53.
[12] Davies, Otter, and Prue, *ibid.*, p. 103.
[13] Beevers and Lipson, *Proc. Roy. Soc.*, 1934, *A*, **146**, 570.

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Brown and Prue [10] to show that, at least for this salt, a q value of about 4 Å was reasonable. Guggenheim [11] favoured larger values of q of the order of 10 Å and suggested that for 2 : 2 electrolytes a value of $C = 2{\cdot}0$ corresponding to $q \sim 9$ Å would be more appropriate. The position in the mixed electrolytes of the present work is complicated since the significance of the q value is uncertain. When recalculations are made with $C = 2{\cdot}0$ in the expression for the activity coefficients of bivalent ions, K for magnesium sulphate at 25° varies by 20—30% in the range of ionic strengths studied. As can be seen in Table 1,

TABLE 1. *E.m.f. measurements.*

Magnesium sulphate

No.	10^3m_1	10^3m_2	No.	10^3m_1	10^3m_2	No.	10^3m_1	10^3m_2
1	5·522	3·619	4	6·170	5·333	7	3·929	34·786
2	7·127	5·222	5	4·392	38·497	8	6·108	21·853
3	7·575	5·148	6	3·652	16·727	9	4·914	19·341

No.	$(E - E^\circ)$	10^3I	$10^3m_{HSO_4^-}$	$10^3m_{M^{2+}}$	$10^3m_{MSO_4}$	K	K (mean)
			Temp. 0°				
1	0·25226	17·59	0·347	3·274	0·345	100	
2	0·24158	24·56	0·567	4·641	0·581	94·4	
3	0·23867	24·66	0·590	4·575	0·573	102	
4	0·24843	24·37	0·512	4·771	0·562	89·2	
8	0·25602	75·46	1·256	17·971	3·882	78·5	
9	0·26542	66·34	0·952	15·846	3·495	82·9	92·0
			Temp. 20°				
1	0·27210	16·73	0·602	3·184	0·435	149	
2	0·26082	22·94	0·947	4·426	0·796	169	
3	0·25771	23·23	0·987	4·401	0·747	163	
4	0·26813	22·20	0·847	4·430	0·903	(183)	160
			Temp. 25°				
1	0·27704	16·46	0·656	3·143	0·475	171	
2	0·26566	22·66	1·032	4·399	0·824	182	
3	0·26249	22·97	1·078	4·387	0·761	188	
4	0·27313	22·00	0·928	4·223	0·911	190	
5	0·30709	101·70	1·889	25·337	13·160	177	
6	0·30838	50·78	1·131	12·279	4·448	166	179
			Temp. 30°				
5	0·31265	94·95	1·981	23·618	14·879	227	
6	0·31406	47·25	1·197	11·451	5·276	224	
7	0·31763	88·46	1·728	21·916	12·870	216	222
			Temp. 35°				
1	0·28706	15·68	0·789	3·027	0·592	247	
2	0·27547	21·71	1·234	4·265	0·957	243	
3	0·27218	22·05	1·284	4·252	0·896	235	
4	0·28338	21·27	1·130	4·358	0·975	(225)	
5	0·31951	92·80	2·128	23·142	15·355	247	
6	0·32030	45·54	1·298	11·084	5·643	257	
7	0·32410	83·75	1·838	20·809	13·977	258	248
			Temp. 40°				
5	0·32622	90·90	2·251	22·862	15·635	(260)	
6	0·32657	43·75	1·394	10·944	5·783	272	
7	0·33055	80·22	1·933	20·130	14·656	290	281
			Temp. 45°				
1	0·29734	15·22	0·942	2·986	0·633	294	
2	0·28548	20·90	1·452	4·190	1·032	295	
3	0·28208	21·51	1·509	4·194	0·954	276	
4	0·29379	20·61	1·336	4·284	1·049	(265)	
5	0·33316	87·41	2·384	21·944	16·550	303	
6	0·33288	42·12	1·385	10·393	6·334	332	
7	0·33683	73·96	2·020	18·505	16·281	374	312

Zinc sulphate

No.	10^3m_1	10^3m_2	No.	10^3m_1	10^3m_2	No.	10^3m_1	10^3m_2
1	7·527	3·571	3	7·664	4·200	5	6·373	4·554
2	6·406	4·554	4	5·328	3·934	6	5·294	4·825

TABLE 1. (*Continued.*)

No.	$(E - E^\circ)$	10^3I	$10^3m_{HSO_4^-}$	$10^3m_{M^{2+}}$	$10^3m_{MSO_4}$	K	K (mean)
			Temp. 0°				
1	0·23783	19·47	0·438	3·205	0·366	120	
2	0·24600	21·38	0·458	3·971	0·583	127	
3	0·23745	21·58	0·506	3·736	0·464	117	
4	0·25419	18·63	0·354	3·500	0·434	113	
5	0·26425	21·39	0·457	3·981	0·573	124	
6	0·25509	21·20	0·405	4·177	0·648	124	121
			Temp. 15°				
3	0·25130	20·53	0·724	3·587	0·613	189	
4	0·26896	17·61	0·512	3·328	0·606	184	
5	0·26068	20·35	0·661	3·828	0·726	182	
6	0·27008	20·14	0·588	4·002	0·823	183	185
			Temp. 20°				
3	0·25605	20·04	0·833	3·513	0·687	223	
4	0·27409	17·28	0·598	3·283	0·651	211	
5	0·26114	19·89	0·765	3·760	0·794	215	
6	0·27531	19·78	0·688	3·962	0·863	234	220
			Temp. 25°				
1	0·26086	17·96	0·792	3·006	0·565	249	
2	0·27032	19·74	0·842	3·754	0·800	225	
3	0·26074	19·83	0·907	3·495	0·706	240	
4	0·27906	16·95	0·650	3·232	0·702	241	
5	0·27053	19·57	0·831	3·711	0·843	240	
6	0·28027	19·14	0·740	3·843	0·982	248	240
			Temp. 35°				
1	0·27049	17·53	0·964	2·984	0·587	288	
2	0·28028	19·08	1·019	3·674	0·880	278	
3	0·27020	19·09	1·084	3·396	0·804	314	
4	0·28930	16·46	0·796	3·178	0·756	288	
5	0·28043	18·77	1·003	3·611	0·943	307	
6	0·29068	18·54	0·904	3·773	1·052	298	295
			Temp. 45°				
1	0·27995	16·89	1·118	2·892	0·679	(394)	
2	0·29047	18·63	1·214	3·648	0·906	319	
3	0·27991	18·65	1·283	3·378	0·822	362	
4	0·29967	15·92	0·948	3·120	0·814	349	
5	0·29062	18·32	1·197	3·593	0·961	345	
6	0·30141	18·17	1·092	3·780	1·045	317	338

TABLE 2. *Thermodynamic properties.*

Reaction	ΔH (kcal. mole^{-1})	ΔG_{298} (kcal. mole^{-1})	ΔS (calc. deg.$^{-1}$ mole^{-1})
Mg^{2+}, SO_4^{2-}	4·84	−3·07	26·2
Zn^{2+}, SO_4^{2-}	4·01	−3·25	24·4

however, the use of $C = 0·2$ yields K values which show no such tendency to drift with ionic strength.

The entropy of association can be written

$$\Delta S = \Delta S_g + \Delta S_{hyd}(MSO_4) - \Delta S_{hyd}(M^{2+}) - \Delta S_{hyd}(SO_4^{2-}) \quad . \quad . \quad . \quad (2)$$

where ΔS_g and ΔS_{hyd} represent gaseous and hydration entropies respectively. $\Delta S_{hyd}(M^{2+})$ and $\Delta S_{hyd}(SO_4^{2-})$ were obtained from the known gaseous and standard entropies,[14] and

$$\Delta S_g = S_{trans}(MSO_4) - S_{trans}(M^{2+}) - S_{trans}(SO_4^{2-}) - S_{rot}(SO_4^{2-}) + S_{rot}(MSO_4)$$

$S_{trans}(MSO_4)$ and $S_{rot}(MSO_4)$ were calculated by the methods described elsewhere [1] with the bond lengths and atomic radii given by Pauling.[15] Values of $\Delta S_{hyd}(MSO_4)$ were

[14] Latimer, "Oxidation Potentials," Prentice-Hall, New York, 1952.
[15] Pauling, "Nature of the Chemical Bond," Cornell Univ. Press, Ithaca, 1939.

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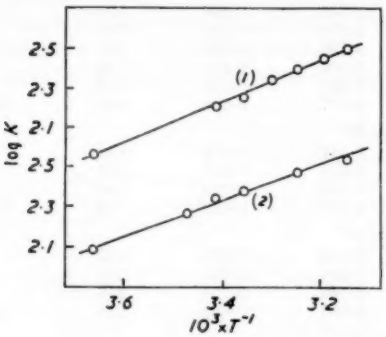
obtained by substitution of the calculated entropies in eqn. (2) and the data are summarised in Table 3 which also includes some values for ion pairs formed between univalent ions. The considerably higher $-\Delta S_{hyd}(MX)$ values for the bivalent sulphates possibly



Plots of log *K against* T^{-1} *for* (1) *magnesium sulphate and* (2) *zinc sulphate.*

TABLE 3. *Thermodynamic properties.*

Ion pair	S_g (MX) (cal. deg.$^{-1}$ mole^{-1})	ΔS (cal. deg.$^{-1}$ mole^{-1})	$S°$ (MX) (cal. deg.$^{-1}$ mole^{-1})	$-\Delta S_{hyd}$ (MX) (cal. deg.$^{-1}$ mole^{-1})
$MgSO_4$	68·8	26·2	3·1	65·7
$ZnSO_4$	70·9	24·4	2·8	68·1
TlCl	60·9	−1·7	41·9	19·0
TlBr	62·8	−4·2	45·5	17·3

reflect a smaller degree of charge neutralisation accompanying their formation than in the case of the thallous ion pairs which are usually considered to be more covalent.

THE UNIVERSITY, GLASGOW, W.2. [*Received, June 10th,* 1958.]

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743. *The Volatile Oil of* Pseudowintera colorata. *Part II.*[1] *The Structure of* cyclo*Colorenone.*

By R. E. CORBETT and R. N. SPEDEN.

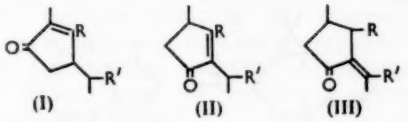
*cyclo*Colorenone, a sesquiterpene ketone present in the volatile oil of *Pseudowintera colorata*, is shown to contain a *cyclo*propane ring, and a constitution is advanced for it.

THE volatile oil of *Pseudowintera colorata*, a shrub endemic to New Zealand, was examined by Findlay,[2] who identified β-phellandrene in the terpene fraction, and by Melville and Levi,[3] who identified α-pinene, (+)-limonene, and dipentene, as well as terpene alcohols and esters, and made a preliminary study of the sesquiterpene fraction. By a precise fractional distillation, Corbett and Grant [1] isolated 30 substances from the oil, including a new sesquiterpene ketone, *cyclo*colorenone.

This communication deals with *cyclo*colorenone, $C_{15}H_{22}O$, the highest-boiling of the sesquiterpenoid components. It has also been obtained by chromatography over alumina of the residues remaining in the still-pot. Altogether it represented 7·5% of the total oil. The infrared spectrum showed the presence of a carbonyl group (1698 cm.$^{-1}$), which the ultraviolet spectrum showed to be conjugated with a double bond ($\lambda_{max.}$ 264 mμ, ε 13,260). Some other structural feature extending conjugation was evidently present since there are no simple αβ-unsaturated carbonyl compounds in which $\lambda_{max.}$ is as high as 264 mμ.

[1] Part I, *J. Sci. Food Agric.*, in the press.
[2] Findlay, *New Zealand J. Sci. Technol.*, 1926, **8**, 107.
[3] Levi and Melville, *J. Soc. Chem. Ind.*, 1932, **51**, 210T.

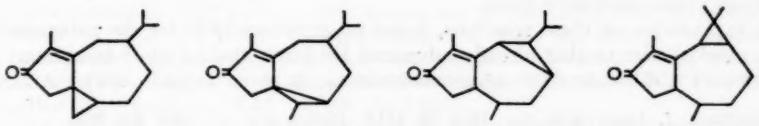
Hydrogenation of *cyclo*colorenone with Adams catalyst could only be achieved under acid conditions, consumption of hydrogen then ceasing at 3·56 mols., and the product was



(I) (II) (III)

a mixture of hydrocarbons. Hydrogenation at high temperatures and pressures with Raney nickel as catalyst gave a number of products, including a mixture of hydrocarbons, an alcohol, *cyclo*coloranol, $C_{15}H_{26}O$, and a ketone, *cyclo*coloranone, $C_{15}H_{24}O$. Oxidation of *cyclo*coloranol with chromic acid [4] gave *cyclo*coloranone, and confirmed the ketonic nature of the carbonyl function. The same ketone was obtained by reduction of *cyclo*colorenone with lithium in liquid ammonia. This ketone showed no selective ultraviolet absorption attributable to ethylenic linkages, and carbonyl absorption at 1747 cm.$^{-1}$ in the infrared spectrum characterised it as a *cyclo*pentanone. *cyclo*Colorenone is therefore a conjugated *cyclo*pentenone (ethylenic band at 1629 cm.$^{-1}$) and, if it contains only one ethylenic linkage, it must be tricyclic. Reduction of *cyclo*colorenone with lithium aluminium hydride gave *cyclo*colorenol, $C_{15}H_{24}O$, and dehydrogenation of this compound with sulphur gave S-guaiazulene,[5] which established the relative positions of the fifteen carbon atoms in the skeleton. *cyclo*Colorenol was oxidised to *cyclo*colorenone by manganese dioxide. The ready interconversion of these two substances under mild conditions makes the possibility of skeletal or double-bond rearrangement remote. *cyclo*Colorenol showed no ultraviolet maximum above 220 mμ, and its infrared spectrum did not contain any bands in the regions characteristic of the C–H deformation and double-bond stretching vibrations of mono-, di-, or tri-substituted ethylenic linkages. Ethylenic linkages in *cyclo*colorenol and *cyclo*colorenone are therefore tetrasubstituted. Three possible *cyclo*pentenone formulations (I, II, and III), based on an S-guaiazulene skeleton, must thus be considered for *cyclo*colorenone.

A choice between these formulations was made by ozonolysis. Under neutral conditions, this afforded acetic acid, indicative of structure (I) unless some extra complication had been introduced.[6] However the ultraviolet absorption maximum expected [6] for structure (I) would be at 240 ± 5 mμ, and not at the observed wavelength 264 mμ. The latter value is greater than any recorded for a *cyclo*pentenone, but is not sufficiently high for an αβ-γδ-unsaturated ketone based on (I). Such a system of conjugated ethylenic linkages is not feasible in any case, since *cyclo*colorenol has no ultraviolet absorption maximum above 220 mμ. The only other structural feature that could extend conjugation without itself being a chromophore is a *cyclo*propane ring, and structures incorporating this group conjugated with the ethylenic linkage (IV, V, VI, and VII) must therefore be considered for *cyclo*colorenone.



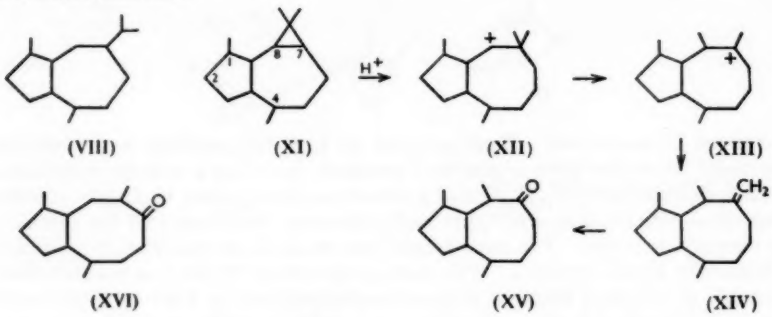
(IV) (V) (IX*) (VI) (X*) (VII) (XI*)

* Saturated hydrocarbon derivatives.

A structure incorporating a *cyclo*propane ring and ethylenic linkage in cross-conjugation with the carbonyl group is not possible, as the ultraviolet spectrum of *cyclo*colorenone

[4] Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2548.
[5] Šorm, Dolejs, Kressel, and Pliva, *Coll. Czech. Chem. Comm.*, 1950, **15**, 83.
[6] Barton and de Mayo, *J.*, 1956, 142.

is not compatible with such a system.[7] Further, the infrared carbonyl absorption of *cyclo*coloranone is consistent with a *cyclo*pentanone, and not a *cyclo*pentanone conjugated with a *cyclo*propane ring.[8]



(VIII) (XI) (XII) (XIII) (XIV) (XV) (XVI)

The hydrogenation results with Adams platinum catalyst are explicable on the basis of these structures, since *cyclo*propane rings in conjugation with ethylenic linkages may be unaffected, partially opened, or completely opened on hydrogenation.[9,10] Structure (IV) is exluded, as the infrared spectra of *cyclo*colorenone and its derivatives do not show a band at 3040—3060 cm.$^{-1}$ (calcium fluoride prism), which has been shown by Cole [11] to be characteristic of the C–H stretching of a CH_2 group in a *cyclo*propane ring. The mixture of saturated hydrocarbons (no light absorption down to 210 mμ) which resulted from the hydrogenation of *cyclo*colorenone was partially soluble (*ca.* 30%) in concentrated sulphuric acid. The insoluble residue $C_{15}H_{28}$, had an infrared spectrum identical with that reported for decahydro-S-guaiazulene (VIII), and physical constants identical with this compound.[12] The compound which dissolved in the sulphuric acid was considered to be a saturated hydrocarbon derived from structure (V, VI, or VII); dissolution in the acid resulted from fission of the *cyclo*propane ring. Confirmation of these views was provided in the following way. The hydrocarbon mixture from the hydrogenation experiment was treated with dry hydrogen chloride, with resultant fission of the *cyclo*propane ring and formation of an exocyclic methylene group (appearance of strong infrared bands at 883 and 1647 cm.$^{-1}$). Ozonolysis of this product gave a ketone, $C_{14}H_{24}O$, together with decahydro-S-guaiazulene. The infrared spectrum of the ketone showed a carbonyl band at 1703 cm.$^{-1}$, corresponding to a *cyclo*heptanone, or a *cyclo*octanone.[13] The saturated hydrocarbon structures corresponding with structures (V, VI, and VII) are designated (IX, X, and XI) respectively. Fission of the *cyclo*propane ring of structure (X) could not lead to a seven- or an eight-carbon ring with an exocyclic methylene group. Likewise fission of the *cyclo*propane ring of structure (IX), while it could lead to a *cyclo*heptane, would almost certainly incorporate a *cyclic* ethylene linkage. Structure (XI) could give rise to an eight-carbon ring system with an exocyclic methylene group.

An explanation of these reactions, based on structure (XI) for the saturated hydrocarbon, and similar to that already advanced by Birch and Lahey [14] to account for the formation of a diketone from *apo*aromadendrone, is given in (XI—XV). Attack by a

[7] Eastman, *J. Amer. Chem. Soc.*, 1954, **76**, 4115; Barton *et al.*, *J.*, 1958, 963, 688.
[8] Eastman *et al.*, *J. Amer. Chem. Soc.*, 1954, **76**, 4115, 4118; Jones and Herling, *J. Org. Chem.*, 1954, **19**, 1252; Josien and Fuson, *Bull. Soc. chim. France*, 1952, **19**, 389; Wiberley and Bunce, *Analyt. Chem.*, 1952, **24**, 623; Barton and Narayanan, *J.*, 1958, 963.
[9] Kazanskii, Malyshev, Aleksanyan, and Sterin, *Chem. Abs.*, 1957, **51**, 4960; *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 1956, 1102.
[10] Kierstead, Linstead, and Weedon, *J.*, 1952, 3610.
[11] Cole, *J.*, 1954, 3807, 3810.
[12] Šorm and Pliva, *Coll. Czech. Chem. Comm.*, 1949, **14**, 274.
[13] Šorm, Dolejs, and Pliva, *Coll. Czech. Chem. Comm.*, 1950, **15**, 187.
[14] Birch and Lahey, *Austral. J. Chem.*, 1953, 379.

proton at position 8 in (XI) would lead through a similar chain of reactions to structure (XVI) for the final ketone. The *cyclo*propane ring fission is not in accordance with Markownikoff's rule. In this case steric factors may be the controlling influence, as the resonance polarisation of the ring would in any case be very small. On the other hand, the ring fission is in accordance with Markownikoff's rule, when *cyclo*colorenol is dehydrogenated to yield S-guaiazulene, and when *cyclo*colorenone is hydrogenated to decahydro-S-guaiazulene. In both cases the direction of opening is governed by the presence of the conjugated ethylenic linkage.

Structure (VII) permits an adequate interpretation of all the experimental observations.

The molecular refraction of *cyclo*colorenone is 66·96. The value calculated by using bond refractions determined by Vogel[15] is 65·40. The exaltation, 1·56, is comparable with that reported for the αβ-unsaturated ketones α-vetivone (1·5), β-vetivone (1·64), and eremophilone (1·37). The observed molecular refractions of the saturated derivatives of *cyclo*colorenone are also in good agreement with calculated values, *viz.*, *cyclo*coloranone obs. 65·97, calc. 65·848, and *cyclo*coloranol, obs. 67·34, calc. 67·404.

Experimental

Infrared spectra were determined on a Perkin–Elmer spectrophotometer model 12 C, as liquid films, or in the case of solids, in Nujol. Alumina, grade H, supplied by Peter Spence & Sons Ltd., was used for chromatography, and all solvents were purified before use.

cyclo*Colorenone*.—This compound was isolated from the residues remaining in the still-pot after the distillation of the essential oil of *Pseudowintera colorata*,[1] by chromatography on alumina. The residue (12·65 g.), in *n*-hexane (30 c.c.), was introduced on to a column of alumina (350 g.), and developed with *n*-hexane. Paraffinic hydrocarbons were eluted with hexane–benzene (19 : 1) (1 l.), and *cyclo*colorenone (6·15 g.) was eluted with hexane–benzene (9 : 1) (1 l.); it had b. p. 136—138°/5 mm., n_D^{20} 1·5270, d_D^{20} 1·0026, $[R_L]_D$ 66·96, $[\alpha]_D^{20}$ −400° (*c* 8·75 in EtOH), $\lambda_{max.}$ 264 mμ (ε 13,260 in EtOH) (Found: C, 82·6; H, 10·05. $C_{15}H_{22}O$ requires C, 82·5; H, 10·15%). cyclo*Colorenone* 2 : 4-*dinitrophenylhydrazone* was scarlet and had m. p. 217—218° after crystallisation from ethyl acetate, $\lambda_{max.}$ 404 mμ (ε 31,490 in $CHCl_3$) (Found: C, 63·65; H, 6·4; N, 14·05. $C_{21}H_{26}O_4N_4$ requires C, 63·3; H, 6·6; N, 14·05%).

Hydrogenation of cyclo*Colorenone*.—(*a*) A solution of *cyclo*colorenone (9·3 g.) in ethanol (200 c.c.), containing Raney nickel (1·5 g.) was shaken with hydrogen in an autoclave at 190°/120 atm. (final) for 27 hr. (disappearance of ultraviolet absorption maximum). Removal of the catalyst and solvent afforded an oil (7·8 g.), which was chromatographed in hexane (20 c.c.) on alumina (250 g.). Hexane (150 c.c.) eluted a mixture of hydrocarbons (3·2 g.) (Found: C, 87·9; H, 11·75. Calc. for $C_{15}H_{24}$: C, 88·15; H, 11·85%). Elution with hexane–benzene (1 : 1) (50 c.c.) gave cyclo*coloranone* (0·36 g.), b. p. 210° (bath-temp.)/7 mm. (Found: C, 81·4; H, 10·9. $C_{15}H_{24}O$ requires C, 81·75; H, 11·0%). cyclo*Coloranone* 2 : 4-*dinitrophenylhydrazone* formed yellow needles, m. p. 191—193° (from ethyl acetate), $[\alpha]_D^{20}$ −43° (*c* 2·15 in $CHCl_3$) (Found: C, 62·8; H, 6·9; N, 13·7. $C_{21}H_{28}O_4N_4$ requires C, 63·0; H, 7·05; N, 14·0%). From the same chromatogram elution with ether–ethanol (9 : 1) (100 c.c.) afforded cyclo*coloranol* as a viscous oil (2·12 g.), b. p. 200° (bath-temp.)/6 mm., n_D^{20} 1·4952, d_4^{20} 0·9614, $[R_L]_D$ 67·34 (Found: C, 81·2; H, 11·75. $C_{15}H_{26}O$ requires C, 81·0; H, 11·8%). cycloColoranol with 3 : 5-dinitrobenzoyl chloride in pyridine–benzene afforded cyclo*coloranyl* 3 : 5-*dinitrobenzoate*, as colourless needles, m. p. 163—165° (from hexane) (Found: C, 63·2; H, 7·05; N, 6·65. $C_{22}H_{28}O_6N_2$ requires C, 63·45; H, 6·8; N, 6·75%).

(*b*) *cyclo*Colorenone (6·1 g.) in ethanol (40 c.c.) containing 3N-hydrochloric acid (0·5 c.c.) was shaken with hydrogen in the presence of Adams catalyst (500 mg.) at atmospheric pressure (3·56 mols. absorbed). After removal of the solvent, the product was percolated in hexane through alumina and distilled; it (5·0 g.) had b. p. 82°/1·5 mm., n_D^{20} 1·4793 (Found: C, 86·95; H, 13·52. Calc. for $C_{15}H_{28}$: C, 86·45; H, 13·55. Calc. for $C_{15}H_{26}$: C, 87·3; H, 12·7%). This product showed no light absorption down to 210 mμ.

[15] Vogel, "A Text Book of Practical Organic Chemistry," Longmans, Green and Co., Ltd., London, 1956, p. 1036.

Decahydro-S-guaiazulene.—The hydrocarbon mixture from the Raney nickel reduction (2·32 g.) was shaken in glacial acetic acid (10 c.c.) and ethanol (25 c.c.) with hydrogen in the presence of Adams catalyst (290 mg.) at atmospheric pressure. 0·4 mol. of hydrogen was consumed. The product (2·1 g.) had b. p. 110°/6 mm., n_D^{20} 1·4827, d_4^{20} 0·8900, $[\alpha]_D^{20}$ −48·02° (Found: C, 87·1; H, 13·1. Calc. for $C_{15}H_{28}$: C, 86·45; H, 13·55. Calc. for $C_{15}H_{26}$: C, 87·3; H, 12·7%). This product showed no light absorption down to 210 mμ. The above product was shaken with concentrated sulphuric acid for 12 hr. and repeatedly extracted with hexane (20 c.c.). The hexane extract was percolated through alumina, and after removal of the hexane, gave decahydro-S-guaiazulene (1·2 g.), n_D^{20} 1·4790, d_4^{20} 0·8850, $[\alpha]_D^{20}$ +9·36° (*c* 1·0 in EtOH) (Found: C, 86·8; H, 13·2. Calc. for $C_{15}H_{28}$: C, 86·45; H, 13·55%). Šorm *et al.*[12] report n_D^{20} 1·4780, d_4^{20} 0·8803.

Oxidation of cyclo*Coloranol.*—*cyclo*Coloranol (1·87 g.) in acetone (30 c.c.) (distilled over potassium permanganate) at 20° was treated with an 8N-solution of chromic acid [chromic oxide (26·7 g.) in concentrated sulphuric acid (23 c.c.) and water (40 c.c.), made up to 200 c.c.], until oxidation was complete (2·1 c.c.). After dilution with water (20 c.c.), the mixture was extracted with ether (3 × 20 c.c.), and the ether solution washed with aqueous sodium carbonate (3 × 100 c.c.) and water (3 × 50 c.c.) and dried (Na_2SO_4). After removal of the ether, the product was absorbed from hexane (30 c.c.) on to alumina (50 g.). Benzene eluted a pale yellow oil, n_D^{20} 1·4911, d_4^{20} 0·9657, $[R_L]_D$ 65·97 (Found: C, 81·8; H, 11·5. Calc. for $C_{15}H_{24}O$: C, 81·75; H, 11·0%), whose infrared spectrum was identical with that of *cyclo*coloranone (CO band at 1747 cm.$^{-1}$).

Reduction of cyclo*Colorenone with Lithium in Liquid Ammonia.*—Lithium (0·63 g.) was dissolved in liquid ammonia (200 c.c.). *cyclo*Colorenone (2·04 g.) in dry ether (50 c.c.) was added during 35 min. After a further 15 min. ammonium chloride was added, the ammonia allowed to evaporate, the residue extracted with ether, and the extract washed with water and dried (Na_2SO_4). Evaporation afforded a brown oil which was absorbed from hexane (20 c.c.) on to alumina (75 g.). Hexane–benzene (4 : 1) eluted *cyclo*coloranone (0·333 g.) (authentic infrared spectrum). The 2 : 4-dinitrophenylhydrazone crystallised from ethyl acetate in yellow needles, m. p. 201—202°, $[\alpha]_D^{20}$ −79° (*c* 2·5 in $CHCl_3$), and had m. p. 198—202° on admixture with the 2 : 4-dinitrophenylhydrazone, m. p. 191—193°, $[\alpha]_D^{20}$ −43° (mixture of stereoisomers), described above.

cyclo*Colorenol.*—To lithium aluminium hydride (0·35 g., 100% excess) in dry ether (50 c.c.) at 0° *cyclo*-colorenone (4·0 g.) in dry ether (60 c.c.) was added during 30 min. (temp. ≯10°). After an additional 30 min., the mixture was cooled to 2°, and water was added dropwise. The ethereal solution was filtered from a granular precipitate, which was in turn triturated with further quantities of ether. The filtrate and washings were washed with distilled water (3 × 100 c.c.) and dried (Na_2SO_4). Removal of the solvent gave cyclo*colorenol* (3·8 g.) which crystallised in needles (from hexane), m. p. 92—93°, $[\alpha]_D^{20}$ −132° (Found: C, 81·75; H, 10·75. $C_{15}H_{24}O$ requires C, 81·75; H, 11·0%).

Oxidation of cyclo*Colorenol.*—*cyclo*Colorenol (0·61 g.) was stirred for 2 hr. with a suspension of manganese dioxide (commercial; 5 g.) in carbon tetrachloride (70 c.c.). Filtration and evaporation afforded a light brown oil (0·55 g.) whose infrared and ultraviolet spectra were identical with those of *cyclo*colorenone. It furnished a 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 216—218° after crystallisation (from ethyl acetate).

Dehydrogenation of cyclo*Colorenol.*—*cyclo*Colorenol (0·28 g.) and finely divided sulphur (0·3 g.) were heated in a nitrate bath for 3 hr. at 220—225°, then extracted with hexane. The hexane solution was shaken with concentrated phosphoric acid. The phosphoric acid extract was diluted with distilled water and then re-extracted with hexane. The hexane solution was washed with water, dried (Na_2SO_4), and evaporated to yield an intensely blue oil, $\lambda_{max.}$ 245, 286, 350, 370 mμ (log ε 4·48, 4·67, 3·75, 3·66), $\lambda_{min.}$ 260, 330, 360 mμ (log ε 4·21, 3·65, 3·57), $\lambda_{max.}$ 605, 660, 730 mμ (ε 430, 354, 127), $\lambda_{min.}$ 650, 720 mμ (ε 346, 112), inflexion, 630 mμ (ε 384). The azulene formed a trinitrobenzene compound, black needles, m. p. 150°, undepressed on admixture with the compound of S-guaiazulene.

Ozonolysis of cyclo*Colorenone.*—*cyclo*Colorenone (200 mg.) in chloroform (25 c.c.) was treated with a stream of ozonised oxygen until the ultraviolet absorption maximum had disappeared. Water (25 c.c.) was added, and the mixture distilled. The distillate was neutralised with aqueous sodium hydroxide, the chloroform removed, and the aqueous residue treated with *p*-bromophenacyl bromide in the usual way. Chromatography of the product in hexane on

deactivated alumina (20 g.) gave *p*-bromophenacyl acetate (29·6 mg.), as colourless plates, m. p. 83—85° (mixed m. p. 84—86°).

Isomerisation and Ozonolysis of Reduced Hydrocarbon.—The hydrocarbon mixture (2·20 g.) from hydrogenation (*b*) above was treated with hydrogen chloride for 1 hr. at 0°, then kept at 0° overnight. The infrared spectrum then showed strong bands at 883 and 1647 cm.$^{-1}$. The product was washed in hexane (20 c.c.) with saturated sodium carbonate solution (3 × 15 c.c.) and with water, and percolated through alumina. After removal of the solvent, the resultant halogen-free (Beilstein test) hydrocarbon (1·846 g.) in acetic acid (25 c.c.) was ozonised for 3 hr. The ozonide was decomposed by water (70 c.c.) and zinc (3 g.). Ether (50 c.c.) was added and the extract washed repeatedly with aqueous sodium carbonate and with water, dried (Na_2SO_4), and evaporated to an oil (1·248 g.), which was chromatographed in hexane on alumina. Hexane (50 c.c.) eluted decahydro-S-guaiazulene (670 mg.) (Found: C, 86·25; H, 13·2. Calc. for $C_{15}H_{28}$: C, 86·45; H, 13·55%). (Infrared spectrum identical with that reported for decahydro-S-guaiazulene.) From the same chromatogram elution with ether (125 c.c.) gave a *ketone* (366 mg.), b. p. 110°/1·0 mm. (Found: C, 81·1, 80·95; H, 11·2, 11·4. $C_{14}H_{24}O$ requires C, 80·7; H, 11·6%) (infrared spectrum, CO band at 1703 cm.$^{-1}$).

One of us (R. E. C.) thanks Professor Sir Alexander Todd, F.R.S., for the privilege of completing this work in his laboratory, and the Nuffield Foundation for a travel grant. This work has been assisted by grants from the Research Fund of the University of New Zealand and from the Mellor Research Fund. Analyses are by Dr. A. D. Campbell of this Department.

CHEMISTRY DEPARTMENT, UNIVERSITY OF OTAGO,
DUNEDIN, NEW ZEALAND.

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NOTES.

744. *Extractives from the New Zealand Myrtaceae. Part III.* Triterpene Acids from the Bark of* Leptospermum scoparium.

By R. E. CORBETT and M. A. MCDOWALL.

TRITERPENE acids have been reported from the bark and heartwood of a number of members of the family Myrtaceae.[1,2] The genus *Leptospermum* is represented in New Zealand by *L. ericoides* (A. Rich), *L. sinclarii*, and *L. scoparium*; the last is the most abundant and widely distributed native tree in New Zealand.

Extraction of the finely powdered outer bark with hexane yielded an amorphous mixture of acids. Fractionation by solvents failed to yield crystalline material, but chromatography on silica gel [3] gave crystalline betulic acid, oleanolic acid, and ursolic acid acetate. Silica gel is an excellent medium for the chromatographic separation of triterpene acids. This appears to be the first reported occurrence of ursolic acid acetate in Nature. Oleanolic acid acetate has been isolated from *Eucalyptus calophylla* bark.[1]

Experimental.—M. p.s are corrected. The silica gel used for chromatography was supplied by the Mallinckrodt Chemical Works, U.S.A. Infrared spectra were determined on a Perkin–Elmer spectrometer model 12C, in Nujol.

Extraction. The fibrous outer bark of *L. scoparium* was stripped from a tree growing near Dunedin, cut into short lengths, and ground to a fine powder (1·0 kg.). It was extracted (Soxhlet) for 48 hr. with hexane (4 l.), the extract was concentrated, the concentrate treated with 20% sodium hydroxide (3 × 200 c.c.), and the insoluble sodium salt (30 g.) dried, dissolved in methanol (800 c.c.) (charcoal), and acidified with concentrated hydrochloric acid (150 c.c.). The precipitated amorphous acid (21 g.) had m. p. 185—200°. Crystallization could not be

* Parts I and II, *J. Sci. Food Agric.*, 1953, **11**, 508, and *J.*, 1954, 1179, respectively.

[1] White *et al.*, *J.*, 1949, 3433; 1952, 5040.
[2] Arthur and Hui, *J.*, 1954, 1403.
[3] Barton and de Mayo, *J.*, 1954, 887.

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effected. Further extraction of the bark with ether, and separation of the acidic material as described, gave more amorphous acid (7 g.). The infrared spectrum of this material was identical with that from the hexane extraction. Neutral compounds from the hexane extract (17 g.) and from the ether extract (15 g.) will be the subject of a future communication.

The acid (14 g.) from the hexane extract, in benzene–ether (9 : 1; 700 c.c.), was introduced on to a column of silica gel (900 g.) made up in hexane. The chromatogram was developed at a pressure of 5 cm. with benzene–ether (19 : 1), and ursolic acid acetate (7·9 g.) was eluted with this solvent (4·3 l.). From the same chromatogram, benzene–ether (10 : 1; 3·3 l.) eluted betulic acid (2·5 g.), closely followed by oleanolic acid (0·77 g.), eluted by the same solvent (2·3 l.).

Ursolic acid acetate, purified by repeated crystallization from 90% aqueous ethanol, had m. p. 285°, $[\alpha]_D^{20}$ +71·5° (*c* 1·9 in chloroform) (Found: C, 77·05; H, 10·3. Calc. for $C_{32}H_{50}O_4$: C, 77·1; H, 10·1%). It formed methyl ursolate acetate, m. p. and mixed m. p. 248—248·5°, and ursolic acid, m. p. and mixed m. p. 295°.

Betulic acid (crystallized from ethanol) had m. p. and mixed m. p. 314°, $[\alpha]_D^{20}$ +5·7° (*c* 1·86 in pyridine). The m. p.s of methyl betulate, 226°, betulic acid acetate, 290°, and methyl betulate acetate, 203—204°, were all undepressed by appropriate authentic derivatives of betulic acid.

Oleanolic acid (recrystallized from ethanol) had m. p. 295—297°, $[\alpha]_D^{20}$ +69° (*c* 0·74 in chloroform), mixed m. p. 300—302° with an authentic specimen, m. p. 305°. It was converted into oleanic acid acetate, m. p. 256°, mixed m. p. 257° with an authentic specimen, m. p. 263°.

One of us (R. E. C.) thanks Professor Sir Alexander Todd, F.R.S., for facilities in his laboratory, and the Nuffield Foundation for a travel grant. We are indebted to Dr. D. E. White of the University of Western Australia for the authentic specimens of the three acids and their derivatives. This work has also been assisted by grants from the Research Fund of the University of New Zealand and from the Mellor Research Fund. Analyses are by Dr. A. D. Campbell of this Department.

UNIVERSITY OF OTAGO, DUNEDIN, NEW ZEALAND. [*Received, May 30th,* 1958.]

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745. *The Fluorescence of Acridine and Acridone Solutions.*

By E. J. BOWEN and J. SAHU.

IT is often stated that acridine is highly fluorescent in alcoholic solution. This fluorescence is, in fact, due almost entirely to the water-content of the alcohol, and the substance is non-fluorescent in most organic liquids; it fluoresces strongly in water. The intensity of fluorescence at different temperatures for mixed solvents of water and alcohols has been studied. The fluorescence intensities diminished with rise of temperature, and the fall increased from the alcohol-rich to the water-rich mixtures. All the results could be empirically represented by $(1/F) - K = k \exp(-E/RT)$, where F is the absolute quantum yield of fluorescence, E an "activation energy of fluorescence quenching" (cal./mole), T the absolute temperature and K and k constants. The results are summarised in the Table.

The values of E are probably correct to $\pm 5\%$, but since K and particularly k depend very much on the choice of E their absolute accuracy is much less.

It is concluded that a hydroxylic environment tends to hold the excited acridine molecule in a rigid form where it has difficulty in losing energy by non-radiational processes.

Solutions of acridone in organic solvents are more fluorescent than those of acridine. In methyl, ethyl, and *iso*propyl alcohols, and in water, over the temperature range −70° to +20°, the quantum yields of fluorescence are practically unity. Solutions in acetone and in ethyl acetate have lower, temperature-dependent, yields and their constants are also given in the Table.

The above expression for the variation of fluorescence yield with temperature follows from the assumption of a temperature-independent radiation process competing with two energy-degradation processes, one temperature-independent and characterised by K

being greater than unity, and the other having a rate constant proportional to $e^{-E/RT}$. The significance of the energy of activation E is not easy to assess, but a consistent scheme seems to be as follows. The excited states of these molecules readily degrade their electronic energies by bending or twisting vibratory movements unless they are bound by inter-

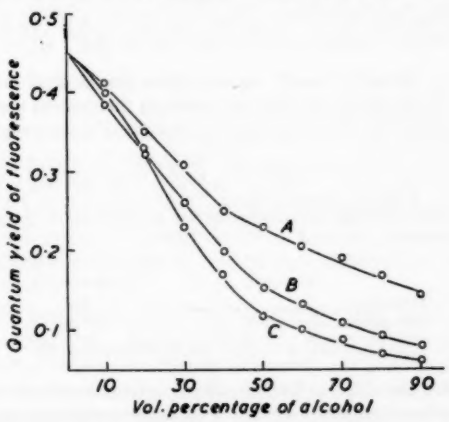
Solutions of acridine in aqueous methanol, ethanol, and glycerol, and of acridone in acetone and ethyl acetate.

Alcohol (%, v/v)	K	$10^{-3}k$	E	Temp. range	K	$10^{-3}k$	E	Temp. range
	Methanol				Ethanol			
0 *	1	6·1	5000	20° to 70°				
10	1·03	7·3	4950	20 to 60	1	7·9	5000	20° to 60°
20	1·1	8·8	4950	20 to 60	1·1	10·5	5000	20 to 60
30	1·2	11	4900	20 to 50	1·4	15	5000	10 to 50
40	1·7	13·4	4900	−20 to 20	1·95	20	5000	−10 to 40
50	2·0	16·4	4850	−30 to 20	3·0	25	5000	−30 to 20
60	2·4	20	4850	−50 to 20	3·4	32	5000	−30 to 20
70	3·1	24	4800	−50 to 20	3·65	40	5000	−50 to 20
80	3·5	30	4800	−50 to 20	4·0	48	5000	−50 to 20
90	5·0	35	4750	−50 to 20	5·5	56	5000	−50 to 20
	Glycerol				Acridone in acetone			
10	1	7	5000	20 to 70	1·0	5·2	4520	−50 to 20
20	1	9·2	5000	20 to 70				
30	1·4	9·2	5000	20 to 70	Acridone in ethyl acetate			
40	2	10	5000	20 to 70				
50	2	14·2	5100	20 to 70	1·0	21	4520	−50 to 20
60	2	20·2	5200	20 to 70				
70	2·7	25·4	5300	20 to 70				
80	2·8	31·8	5400	20 to 70				
90	4·0	37·4	5500	20 to 70				

* *I.e.*, pure water.

molecular forces to solvent molecules. Such binding, assisted by high solvent viscosity (as in glycerol solutions), appears to limit the amplitudes of vibratory movements, and to make activation energy necessary for electronic energy degradation to occur.

Experimental.—Fluorescence intensities of solutions were measured in an apparatus already described,[1] which was designed to minimise errors due to refractive-index changes and other



Fluorescence intensity of water–alcohol solutions of acridine at 20°.

Fluorescence intensity of acridine in aqueous solutions of A, glycerol; B, methanol; C, ethanol.

complicating effects. The solution, at a concentration giving practically total light absorption, was illuminated in a tube at the centre of a whitened and evacuated spherical flask which acted as an integrating sphere and a Dewar vessel, and the fluorescence was collected from

[1] Bowen and Sahu, *J. Phys. Chem.*, 1958, in the press.

part of the flask wall by a calibrated photomultiplier–spectrograph combination. Using solutions of known absolute yield [2] we could obtain the fluorescence yields of the solutions by comparison of properly corrected fluorescence-band areas. Results for acridine in mixtures of water with methyl and ethyl alcohols and with glycerol at 20° are shown in the Figure. Dissolved air had only a small effect on the fluorescence. Measurements were also made of these solutions over such parts of the temperature range −50° to +60° as freezing points or high vapour pressures allowed.

PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, November 26th*, 1957.]

[2] Weber and Teale, *Trans. Faraday Soc.*, 1957, **53**, 646.

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746. *Tracer Studies in Ester Hydrolysis. Part VII.* The Hydrolysis of 9-Fluorenyl Acetate.*

By C. A. BUNTON, G. ISRAEL, M. M. MHALA, and D. L. H. WILLIAMS.

IN Part IV of this series [1] results were reported of a mechanistic study of the hydrolysis of diphenylmethyl formate in acid, alkaline, and initially neutral solution, and of diphenylmethyl acetate in acid solution. This communication describes a study of the hydrolysis of the structurally similar 9-fluorenyl acetate, and an extension of the earlier work to the alkaline hydrolysis of diphenylmethyl acetate. The kinetic effect of the substitution of deuterium for protium on the alkyl-carbon atom of these esters has also been examined.

The S_N1 reactivity of an alkyl halide often indicates qualitatively the ease of alkyl–oxygen bond fission in the corresponding carboxylic ester. It has recently been suggested, on the basis of kinetic solvent effects and the variation of the Arrhenius parameters for the acid hydrolyses of various carboxylic esters of diphenylmethanol, that the alkyl–oxygen bond is broken in certain experimental conditions.[2] However our tracer experiments did not detect any alkyl–oxygen bond fission in diphenylmethyl formate or acetate; but a small component in the acetate might have been obscured by oxygen exchange between diphenylmethanol and the water of the solvent.

As a possible explanation of the acyl–oxygen bond fission in diphenylmethyl formate and acetate it was suggested that there might be intramolecular hydrogen bonding between the carbonyl-oxygen atom and a hydrogen atom on the alkyl-carbon atom. It was hoped that examination of the hydrolysis of 9-fluorenyl acetate, and of the kinetic effect of deuterium substitution in the " alkyl " group, might provide useful information.

Results.—Bond fission. The position of bond fission was determined by isolating the alcohol product with the water of the solvent enriched in ^{18}O (Table 1). The acyl–oxygen bond is broken in the alkaline hydrolysis of 9-fluorenyl acetate, and the same bond fission is assumed

TABLE 1. *Bond fission in the hydrolysis of 9-fluorenyl acetate.*

Solvent: dioxan–water 70 : 30 v/v. Temp. 100°, except for the alkaline hydrolysis which was at 25°. Isotopic abundance of water 0·790 atom % excess. Abundance of alcohol in terms of atom % excess.

	Hydrolyses			Control	
Reagent	0·4M-NaOH	0·5M-H_2SO_4	(Neutral)	0·05M-H_2SO_4	0·2M-AcOH
Time (hr.)	10	15	1600	15	1600
Abundance of alcohol	0·030	0·140	0·056	0·250	0·014

[9-Fluorenyl acetate]: *ca.* M/3 in hydrolysis. [Fluoren-9-ol]: *ca.* M/3 in control experiments.

for the alkaline hydrolysis of diphenylmethyl acetate, by analogy with results for 4-methoxydiphenylmethyl acetate [3] and diphenylmethyl formate.[1] A similar result is found, within the limits imposed by oxygen exchange between the alcohol and water, for the acid hydrolyses of

* Part VI, *J.*, 1958, 3248.

[1] Bunton, Day, Flowers, Sheel, and Wood, *J.*, 1957, 963.
[2] Harvey and Stimson, *J.*, 1956, 3629.
[3] Bunton and Hadwick, *J.*, 1957, 3013.

9-fluorenyl and diphenylmethyl acetate.[1] The fluoren-9-ol from hydrolysis in initially neutral solution is slightly enriched in ^{18}O; this may correspond to a minor contribution by mechanism $B_{Al}1$.

Kinetic form for hydrolysis. The hydrolysis is accelerated by hydrogen and hydroxide ions. In initially neutral solution there is a slow hydrolysis which is not autocatalysed, and therefore is a reaction of the ester molecule with water. The acid hydrolysis follows the law, Rate = $k_A[H^+][Ester]$, with $10^3k_A = 2{\cdot}58$ (sec.$^{-1}$ mole^{-1} l.) at 100·1°. The Arrhenius equations are: acid, $k_A = 1{\cdot}1 \times 10^7 \exp(-16{,}400/RT_A)$; alkaline, $k_2 = 2{\cdot}4 \times 10^8 \exp(-13{,}400/RT_A)$; neutral, $k_1 = 4{\cdot}2 \times 10^{11} \exp(-29{,}900/RT_A)$. The rates are similar to those for diphenylmethyl acetate, and are unaffected by deuterium substitution on the alkyl-carbon atom.

TABLE 2. *Rates of hydrolysis in aqueous dioxan.*

Solvent: dioxan–water 70 : 30 v/v. Protio-compound unless otherwise specified.

(A) 9-*Fluorenyl acetate.*

(i) Alkaline hydrolysis at 25° (except where otherwise specified).

	Protio			Deutero	
10^2k_2 (sec.$^{-1}$ mole^{-1} l.)	3·57 [a]	3·60 [b]	0·45 [a]	3·75 [c]	3·69 [b]

[a] Temp. 0°. [a, c] Conductimetric, mean of 5 and 2 values respectively. [b] Titration, mean of 2 values.

(ii) Acid hydrolysis at 100·1° (except where otherwise specified).

$[H_2SO_4]$ (M) ...	0·0239	0·0396	0·0406	0·0496		0·0506	0·0570	0·0706	0·074
10^4k_1 (sec.$^{-1}$)	0·54	0·94	1·06	1·23	1·20 †	1·28	1·48	1·73	0·0398 [a]

[a] Temp. 44·6°. † Deutero compound.

(iii) Neutral hydrolysis.

At 100·1° $10^6k_1 = 1{\cdot}35$ (sec.$^{-1}$); at 82·0° $10^7k_1 = 1{\cdot}73$ (sec.$^{-1}$).

(B) *Diphenylmethyl acetate.*

Alkaline hydrolysis at 25°.

	Protio		Deutero
10^2k_2 (sec.$^{-1}$ mole^{-1} l.)	1·20 [a]	1·21	1·19

[a] Conductimetric, mean of two values; other values were obtained by titration.

Discussion.—The position of bond fission and the kinetic form show that the mechanism of the alkaline hydrolysis of diphenylmethyl and 9-fluorenyl acetate is $B_{Ac}2$. Similarly, in acid solution the acyl–oxygen bond is broken in the hydrolysis of 9-fluorenyl acetate. The Arrhenius parameters are in the range considered to be typical of acid-catalysed bimolecular hydrolyses.[2,4]

The value of k_2 for the basic hydrolysis of 9-fluorenyl acetate is *ca.* three times that for diphenylmethyl acetate, which is itself very similar to that for the 4-methoxydiphenylmethyl acetate.[3] The rate of nucleophilic attack on the acyl-carbon atom of a carboxylic ester is little affected by the electronic properties of the alkyl group; it is much more sensitive to the nature of the group attached to the reaction centre. Probably the slightly greater reactivity of 9-fluorenyl acetate is caused by the greater electron-attraction of the fluorenyl than of the diphenylmethyl group. Diphenylmethyl formate is much more reactive towards hydroxide ions than is the acetate;[1] similar rate differences are observed for the aliphatic series.

The rates of acid hydrolysis of 9-fluorenyl and diphenylmethyl acetate are very similar, but the diphenylmethyl ester is the more reactive. The factor is *ca.* three (Table 2), although the conditions of hydrolysis of the two esters are slightly different. It is not easy to interpret such small rate differences for reactions with specific hydrogen-ion catalysis, because the rate equation is made up of an equilibrium constant for the formation of the conjugate acid and a rate constant for its breakdown to products. The effects of structural changes on these constants cannot, in general, be evaluated independently, and electronic displacements may affect these constants in opposite directions. However the mechanism

[4] Long and Pritchard, *J. Amer. Chem. Soc.*, 1957, **79**, 2365.

$A_{Ac}2$, like $B_{Ac}2$, is not usually much affected by the electronic properties of the alkyl group.[5] Again the formate is more reactive than the acetate.[1]

It was suggested earlier [1] that the reactivity of the acyl-carbon atom of a carboxylic ester might be increased by hydrogen bonding between the carbonyl-oxygen atom and a hydrogen atom attached to the alkyl-carbon atom. The similarity of the rates of hydrolysis of 9-fluorenyl and diphenylmethyl acetate, in both acid and alkaline solution, suggests that there is no catalysis by such an intramolecular hydrogen bonding. This conclusion is strengthened by the negligible effect which the replacement of protium by deuterium has on the rates of both acid- and base-hydrolysis, because the extent of an intramolecular hydrogen-bonding, and therefore the rates of hydrolysis, should be affected by such a substitution. It is conceivable, but unlikely, that the change in stability which replacement of protium by deuterium brings about in the initial state, is very close to that which it brings about in the transition state, but it is much simpler to believe that interactions between the carbonyl-oxygen atom and hydrogen atoms of the alkyl group are not kinetically significant in ester hydrolyses. (Any inductive, or other, effect of deuterium relayed through the carbon and oxygen atoms would have a negligible kinetic effect at the acyl-carbon atom.[6])

Experimental.—Materials. Deuterated diphenylmethanol and fluoren-9-ol were prepared by reduction of corresponding ketones with lithium aluminium deuteride in dry ether. The aluminium complex was destroyed by the cautious addition of isotopically normal water. Diphenylmethyl [^{2}H]alcohol, recrystallised from light petroleum, had m. p. 66—67° (yield 80%). Fluoren-9-[^{2}H]ol, recrystallised from aqueous ethanol, had m. p. 152—153° (yield 95%).

Fluoren-9-ol, prepared by reduction of the ketone with lithium aluminium hydride, had m. p. 155°.

The acetates, prepared by use of acetic anhydride, were decolorised with charcoal and recrystallised from light petroleum. Diphenylmethyl acetate had m. p. 42°; its deutero-analogue had m. p. 41—42°; 9-fluorenyl acetate had m. p. 70°; its deutero-analogue had m. p. 69—70°.

Solvents were made up by weight from purified dioxan and water to correspond to dioxan–water 70 : 30 v/v.

Position of bond fission. Tracer experiments were made with the solvent water enriched in ^{18}O. The alcohol, isolated from hydrolysis under kinetically controlled conditions, was purified by recrystallisation from light petroleum, and dried in a vacuum-desiccator. The isotopic abundance of samples was determined by pyrolysing them *in vacuo* on a carbon tube heated by an R.F. induction furnace. The carbon monoxide so produced was analysed mass-spectrometrically.

Kinetic runs. The hydrolyses were followed by acid–base titration for acid, alkaline, and initially neutral solutions. Some runs in alkaline solution were followed conductimetrically.[7] Stoppered flasks or cells were used for experiments at ⩽25°; sealed tubes were used at the higher temperatures.

Two runs on protio- and deutero-diphenylmethyl acetate are detailed.

Temp. 25°. Followed by acid base titration.
Initial $[OH^-] = 4{\cdot}00 \times 10^{-3}$M; [protio-ester] $= 2{\cdot}38 \times 10^{-2}$M; [deutero-ester] $= 2{\cdot}35 \times 10^{-2}$M.

Time (min.)	0	4	9	16	22	31·5	32	44	58	78
$[OH^-]$	18·32	16·80	15·29	14·11	13·36	—	12·11	11·18	10·43	9·64
[Protio-ester]	10·90	9·38	7·87	6·69	5·94	—	4·69	3·76	3·01	2·22
$[OH^-]$	18·32	16·53	15·31	14·08	13·26	12·31	—	11·20	10·40	9·62
[Deutero-ester] ...	10·79	9·00	7·78	6·55	5·73	4·78	—	3·67	2·87	2·09

(Concn. expressed as c.c. of 0·0218N-HCl per 10 c.c. portion of reaction mixture.)

10^3k_2 (sec.$^{-1}$ mole^{-1} l.): protio 1·21; deutero 1·19 (calcd. graphically from the integrated second-order rate equation).

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, GOWER STREET, LONDON, W.C.1. [*Received, March 13th*, 1958.]

[5] Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686.
[6] Halevi, *Tetrahedron*, 1957, **1**, 174.
[7] Daniels, Mathews, Williams, Bender, and Alberty, "Experimental Physical Chemistry," McGraw-Hill, New York, 1956, p. 131.

747. N-*Oxides and Related Compounds. Part XV.*[1] *Ultraviolet Spectra of 2′-(Carbamoyl- and Ethoxycarbonyl-)vinylpyridines and their* 1-*Oxides.*

By A. R. Katritzky, A. M. Monro, and J. A. T. Beard.

Dipole moments of 4-substituted derivatives show that the pyridine 1-oxide ring can create both a deficit and a surfeit of electrons at the 4-position more readily than the pyridine ring.[2] Carbonyl-stretching frequencies in acyl derivatives show in addition that the pyridine 1-oxide ring can make electrons available more readily in the 4- than in the 3-position, but that the reverse is true of the pyridine ring.[3] To study the effect of these differences on ultraviolet spectra, we examined the isomeric β-pyridylacrylic esters and amides and their 1-oxides (Table); the acids were not used because of complications from zwitterion formation.

Ultraviolet spectra (λ *in* mμ).

	Neutral molecule [a]						Conjugate acid [b]			
Subst.	λ	$10^3\varepsilon$	λ	$10^3\varepsilon$	λ	$10^3\varepsilon$	λ	$10^3\varepsilon$	λ	$10^3\varepsilon$
(A) *Ethyl β-substituted acrylates.*										
Ph	204	11·9	217 222 *	13·1 11·2	279	21·6	(Not applicable)			
4-Pyridyl ...	204	13·3	—	—	259	21·9	—	—	271	23·4
3-Pyridyl ...	206	12·5	262	17·1	282 *	13·5	218 *	13·0	255 280 *	18·0 9·9
2-Pyridyl ...	206	14·5	249	12·7	290	15·0	206 241	14·4 8·4	290	18·6
(B) *Ethyl β-substituted acrylate* N-*oxides.*										
4-Pyridyl ...	221	12·4	—	—	300	18·9	203	15·1	278	23·2
3-Pyridyl ...	206	10·4	—	—	252	28·6	223	17·4	261	15·4
2-Pyridyl ...	—	—	244	26·7	286	13·2	216 251	14·2 8·4	294	15·4
(C) *β-Substituted acrylamides.*										
Ph	204	16·4	216 222 *	18·6 16·4	275	23·9	(Not applicable)			
4-Pyridyl ...	205	14·4	—	—	259	21·7	—	—	271	23·2
3-Pyridyl ...	206	13·4	259	19·0	284 *	13·4	224	14·7	255	23·4
2-Pyridyl ...	206	16·0	249	14·6	289	15·2	206 241	14·2 9·9	291	18·0
(D) *β-Substituted acrylamide* N-*oxides.*										
4-Pyridyl ...	221	13·5	—	—	300	20·7	207	13·8	282	24·6
3-Pyridyl ...	—	—	—	—	251	28·9	222	14·1	265	16·4
2-Pyridyl ...	—	—	239	28·7	281	13·6	221 256 *	14·0 9·3	296	16·6

* Inflection. [a] In aqueous phosphate buffer of pH 9·7, except that the first entry is for aqueous ethanol (70 : 30 v/v), and the eighth for water. [b] Entries nos. 2—4 and 9—11 in aqueous N-sulphuric acid, others in 20N-sulphuric acid.

In these compounds, the band of longest wavelength probably corresponds to a π–π^* transition, the promotion of an electron between molecular orbitals including both the ring and the side chain. The greater the conjugation between ring and side chain, the lower will be the energy of the first excited state, and thus the longer the wavelength of the bands. The side chains act as electron-acceptors more readily than electron-donors; in agreement, the wavelength is longer, and the conjugation thus stronger, in the 4- than in the 3-pyridine 1-oxide, but in the 3- than in the 4-pyridine (see Figure). In the conjugate acids, the electron-donor ability of the rings is much impaired; the conjugation is probably

[1] Part XIV, Katritzky and Hands, *J.*, 1958, 2195.
[2] Katritzky, Randall, and Sutton, *J.*, 1957, 1769; Bax, Katritzky, and Sutton, *J.*, 1958, 1254.
[3] Katritzky, Monro, Beard, Dearnaley, and Earl, *J.*, 1958, 2182.

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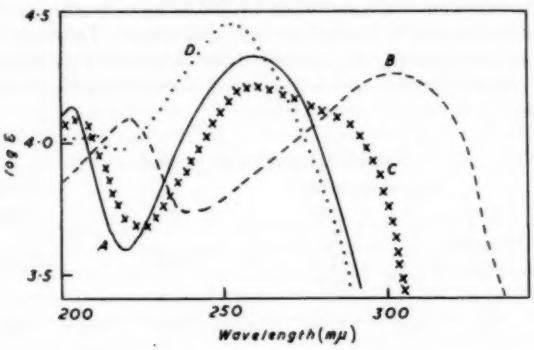
mainly by donation of electrons from the side chain to the ring. In agreement the wavelength is longer in the order 2 > 4 > 3 for both the pyridines and the 1-oxides, and in each one of these positions the 1-oxide absorbs at longer wavelengths than the corresponding pyridine. Donation to the ring may be important in both the 2-substituted compounds, even in the neutral molecules. These results parallel those for the infrared C:C stretching band.[3]

Ultraviolet spectra of (A) ethyl 4-pyridylacrylate, (B) its 1-oxide, and (C) ethyl 3-pyridylacrylate and (D) its 1-oxide.



Experimental.—Preparation of the 3- and the 4-pyridyl compounds has been described.[4,5] Ethyl cinnamate was a redistilled commercial sample; the amide was prepared by a standard method.

β-2-*Pyridylacrylamide.* Ethyl β-2-pyridylacrylate (62%), b. p. 159°/22 mm. (lit.,[6] b. p. 161/25 mm.), was prepared as for the 4-analogue;[4] with aqueous-ethanolic ammonia it gave the *amide* (96%), rhombs (from ethanol), m. p. 141° (Found: C, 64·5; H, 5·4. $C_8H_8ON_2$ requires C, 64·8; H, 5·4%).

Oxidation[5] of the above ester gave the *ethyl ester 1-oxide* (56%), rhombs (from ethyl acetate or benzene), m. p. 68—68·5° (Found: C, 61·9; H, 5·9; N, 7·1. $C_{10}H_{11}ON_3$ requires C, 62·2; H, 5·7; N, 7·3%), which afforded (as above) the *amide 1-oxide* (67%), prisms (from ethanol), m. p. 208—209° (darkens above 200°) (Found: C, 58·3; H, 5·0; N, 17·0. $C_8H_8O_2N_2$ requires C, 58·5; H, 4·9; N, 17·1%).

Oxidation[5] gave the *acid 1-oxide* (52%), which separated from pentyl alcohol in needles, m. p. 240° (decomp.; darkens above 225°) (Found: C, 58·4; H, 4·1; N, 8·4. $C_8H_7O_3N$ requires C, 58·2; H, 4·3; N, 8·45%).

This investigation was largely carried out during the tenure (by A. R. K.) of an I.C.I. Fellowship. The spectra were measured by Miss V. Brown, under the supervision of Dr. F. B. Strauss, on a Cary recording spectrophotometer.

THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY.
THE CHEMICAL LABORATORY, CAMBRIDGE UNIVERSITY. [*Received, March 17th*, 1958.]

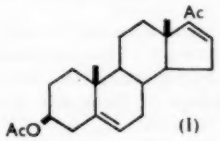
[4] Katritzky, *J.*, 1955, 2581.
[5] Katritzky and Monro, *J.*, 1958, 150.
[6] Löffler and Flügel, *Ber.*, 1909, **42**, 3423.

748. *The Michael Reaction of 3β-Acetoxypregna-5 : 16-dien-20-one and Malonic Ester.*

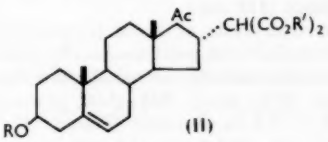
By Peter Bladon.

The ability of a wide variety of nucleophilic reagents to add to the double bond of Δ^{16}-unsaturated 20-oxo-steroids is well known. Thus, reactions with alkoxides,[1] amines,[2] and thiols[3] lead to the formation of 16α-alkoxy-, 16α-alkylamino-, and 16α-alkylthio-derivatives, respectively. Nitroparaffins under appropriate conditions[4] give 16α-nitroalkyl derivatives. The possibility that derivatives of progesterone containing carboxyl or methoxycarbonyl functions might have useful biological properties prompted extension of this type of reaction.

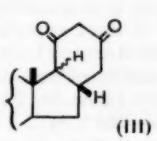
Michael reaction between 3β-acetoxypregna-5 : 16-dien-20-one (I) and sodiomalonic ester gave, after brief hydrolysis with aqueous alkali and acid treatment, the expected 3β-hydroxy-20-oxopregn-5-en-16α-ylmalonic acid (IIa). If the hydrolysis step was omitted, the product was the ethyl ester (IIb) which was, however, not obtained crystalline. Prolonged hydrolysis resulted in poor yields of the acid, due to (*a*) the splitting of the product into hydrolysed starting materials and (*b*) further changes to an amorphous product from which a small amount of crystalline material was obtained. The tentative formulation of this as (III) is supported by the fact that the ultraviolet spectra in neutral and alkaline solution resemble the corresponding spectra of 5 : 5-dimethyl*cyclo*hexane-1 : 3-dione (dimedone). Further, the infrared spectrum had a strong band at 1590 cm.$^{-1}$, characteristic of the enol form of a β-diketone. The ill-defined melting point and poor recovery on crystallisation are probably due to the presence of (C-17) isomeric substances, and two enol forms.



(I)

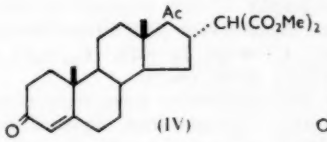


(II)



(III)

(IIa; R = R′ = H)
(IIb; R = Ac or H, R′ = Et)
(IIc; R = H, R′ = Me)
(IId; R = Ac, R′ = Me)
(IIe; R = B_3, R′ = Me)



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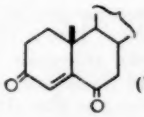
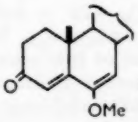


(V)



(VI)

Oxidation of the methyl ester (IIc) by chromic acid–sulphuric acid in acetone,[5] gave either of two products depending on the amount of oxidant used. The first, obtained with 1 mole of oxidant, was a mixture of the Δ^5-3-ketone and starting material. This

[1] Gould, Gruen, and Hershberg, *J. Amer. Chem. Soc.*, 1953, **75**, 2510; Hirschmann, Hirschmann, and Daus, *ibid.*, 1952, **74**, 539.
[2] Gould, Shapiro, and Hershberg, *ibid.*, 1954, **76**, 5567.
[3] Rosenkranz, Djerassi, and Romo, U.S.P. 2,697,108 (*Chem. Abs.*, 1955, **49**, 14044).
[4] Dodson, U.S.P. 2,697,109 (*Chem. Abs.*, 1955, **49**, 14042).
[5] Djerassi, Engle, and Bowers, *J. Org. Chem.*, 1956, **21**, 1547; Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402.

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was treated with mineral acid, to yield, after purification, the desired dimethyl 3 : 20-dioxopregn-4-en-16α-ylmalonate (IV). Excess of oxidant gave dimethyl 3 : 6 : 20-trioxopregn-4-en-16α-ylmalonate (V), which on treatment with acidic methanol gave dimethyl 6-methoxy-3 : 20-dioxopregna-4 : 6-dien-16α-ylmalonate (VI), whose ultraviolet absorption spectrum shows peaks at 205, 249, and 304 mμ. Windaus, Inhoffen, and Reichel [6] record a spectrum with peaks at 247 and 295 mμ (in ether) for 6-ethoxycholesta-4 : 6-dien-3-one, formed analogously from cholest-4-ene-3 : 6-dione and acidic ethanol.*

Experimental.—M. p.s were determined on a Kofler hot stage. Unless otherwise stated rotations were determined in chloroform at room temperature, ultraviolet spectra in ethanol, and infrared spectra as Nujol mulls.

3β-*Hydroxy*-20-*oxopregn*-5-*en*-16α-*ylmalonic Acid* (IIa). Sodium (200 mg., 8 mmoles) was dissolved in ethanol (25 ml.) and diethyl malonate (1·6 g., 10 mmoles) was added followed by 3β-acetoxypregna-5 : 16-dien-20-one (712 mg.; 2 mmoles). The mixture was refluxed for 3 hr. with exclusion of moisture; then a solution of potassium hydroxide (4 g.) in 50% v/v aqueous ethanol (20 ml.) was added and refluxing continued for 5 min. Addition of water and extraction with ether afforded a small neutral fraction (4 mg.). Acidification of the aqueous layer gave a white solid (782 mg.). Recrystallisation of the dried material from methanol–acetone gave 3β-*hydroxy*-20-*oxopregn*-5-*en*-16α-*ylmalonic acid* (IIa) as needles, m. p. 250—253°, $[\alpha]_D$ +36° (*c*, 0·40 in methanol) (Found: C, 68·55; H, 8·25. $C_{24}H_{34}O_6$ requires C, 68·9; H, 8·2%); $\nu_{max.}$ 1740 m, 1700 m, and diffuse peaks at 3460 and 3220 cm.$^{-1}$.

If the reaction mixture was extracted with ether after the initial refluxing, there was isolated the corresponding diethyl ester (IIb) as an oil (866 mg.), and an acidic fraction (243 mg., soluble in aqueous potassium hydrogen carbonate). Brief hydrolysis of the neutral ester gave the acid in good yield. Hydrolysis of the acidic fraction gave an amorphous acidic material which was probably identical with material described below.

In another experiment (on half the scale) hydrolysis for 2 hr. under reflux gave a neutral fraction (219 mg.) from which 3β-hydroxypregna-5 : 16-dien-20-one could be isolated together with the acid described above (118 mg.).

In a third experiment, hydrolysis at room temperature overnight afforded a negligible amount of neutral fraction together with gelatinous acidic material (750 mg.). Recrystallisations from methanol and dimethylformamide–methanol gave rhombs of 3β-*hydroxy*-16α : 24-cyclo-21-*norchol*-5-*en*-20 : 23-*dione* (III), m. p. 235—245° (decomp.) (change of form into needles at 200—220°), $[\alpha]_D$ +55·4° (*c* 0·5 in pyridine) (Found: C, 74·3; H, 8·95. $C_{23}H_{32}O_3,CH_3OH$ requires C, 74·2; H, 9·3%); $\lambda_{max.}$ 254·5 mμ, ε 14,000; $\lambda_{max.}$ (at pH 9·5) 285 mμ, ε 22,000; $\nu_{max.}$ 1700 w, 1640 w, 1590 s and a broad hydroxyl peak in the 3000 cm.$^{-1}$ region. Dimedone under similar conditions had $\lambda_{max.}$ 257 mμ, ε 16,600 and $\lambda_{max.}$ (at pH 9·5) 282 mμ, ε 25,700.

Dimethyl 3β-*hydroxy*-20-*oxopregn*-5-*en*-16α-*ylmalonate* (IIc). The foregoing acid (2·08 g.; m. p. 200—250°) suspended in a little methanol was treated with excess of diazomethane in ether for 20 min. After destruction of diazomethane the solution was evaporated to dryness. Crystallisation from methanol–ether and chromatography of the material in the mother liquors gave material, m. p. 200° (969 mg.). The pure *dimethyl ester* (IIc) formed needles, m. p. 200—202°, $[\alpha]_D$ +22° (*c* 0·38), from acetone (Found: C, 69·95; H, 8·75. $C_{26}H_{38}O_6$ requires C, 69·95; H, 8·6%); $\nu_{max.}$ 3560 w, 3500 w, 1740 s, 1720 s, 1698 s cm.$^{-1}$.

Acetylation of this ester with acetic anhydride and pyridine at room temperature gave *dimethyl* 3β-*acetoxy*-20-*oxopregn*-5-*en*-16-*ylmalonate* (IId), crystals from aqueous methanol, m. p. 124—125° (solidifying and remelting at 138—139°), $[\alpha]_D$ +8·8° (*c* 0·69) (Found: C, 69·0; H, 8·6. $C_{28}H_{40}O_7$ requires C, 68·8; H, 8·25%); $\nu_{max.}$ 1741, 1710, 1225 cm.$^{-1}$. The *benzoate* (IIe) prepared with benzoyl chloride and pyridine formed needles, m. p. 200—201°, $[\alpha]_D$ +32·6° (*c* 0·59), from acetone–methanol (Found: C, 71·75; H, 7·8. $C_{33}H_{42}O_7$ requires C, 72·0; H, 7·7%); $\nu_{max.}$ 1741, 1700, 707 cm.$^{-1}$.

Dimethyl 3 : 20-*dioxopregn*-4-*en*-16α-*ylmalonate* (IV). Dimethyl 3β-hydroxypregn-5-en-16α-ylmalonate (223 mg.) in acetone (15 ml.) was stirred vigorously at room temperature and chromic acid solution added (0·15 ml. of a solution of 66·7 g. of chromium trioxide and 53 ml. of concentrated sulphuric acid made up to 250 ml. with water). After 1 min., methanol was

* The author is very grateful to a Referee for pointing out the analogy with Windaus's compound.

[6] Windaus, Inhoffen, and Reichel, *Annalen*, 1934, **510**, 248.

added followed by water in excess. The product was isolated by extraction with ether, the extracts being washed with aqueous potassium hydrogen carbonate, and dried (Na_2SO_4). The residue (215 mg.) in methanol (15 ml.) was warmed with 10% aqueous sulphuric (2 ml.) for 10 min. Addition of water and extraction with ether (as before) afforded a solid residue. Chromatography on alumina (5 g.) gave *dimethyl* 3 : 20-*dioxopregn*-4-*en*-16α-*ylmalonate* (IV) (105 mg.), eluted with benzene, and forming prisms (from dichloromethane–*iso*propyl ether), m. p. 142—145°, $[\alpha]_D$ +117·5° (*c* 0·62) (Found: C, 70·45; H, 8·4. $C_{26}H_{36}O_6$ requires C, 70·25; H, 8·15%); $\lambda_{max.}$ 240 mμ, ε 15,700; $\nu_{max.}$ 1764, 1745, 1706, 1681, 1621 cm.$^{-1}$. Elution of the column with ether gave starting material, m. p. 200—202° (42 mg.).

Dimethyl 3 : 6 : 20-*trioxopregn*-4-*en*-16α-*ylmalonate* (V). To vigorously stirred dimethyl 3β-hydroxypregn-5-en-16α-ylmalonate (203 mg.) in acetone (10 ml.) the foregoing chromic acid solution (1 ml.) was added at 20°. The excess of oxidant was destroyed after 5 min. by adding dilute hydrochloric acid and sodium sulphite. Ether extraction gave a solid (144 mg.) which on crystallisation from methanol gave *dimethyl* 3 : 6 : 20-*trioxopregn*-4-*en*-16α-*ylmalonate* as pale yellow prisms, m. p. 171—172°, $[\alpha]_D$ +11·9° (*c* 0·72) [Found: C, 67·8; H, 7·8%; *M* (Rast), 478. $C_{26}H_{34}O_7$ requires C, 68·1; H, 7·5%; *M*, 459]; $\lambda_{max.}$ 252 mμ, ε 11,600; $\nu_{max.}$ 1759—1737, 1691, and 1607 cm.$^{-1}$.

Dimethyl 6-*methoxy*-3 : 20-*dioxopregna*-4 : 6-*dien*-16α-*ylmalonate* (VI). The foregoing triketone (75 mg.), in methanol (5 ml.), was treated with perchloric acid (2 drops of 70% aqueous solution) and warmed. After 5 min. water was added, and the product isolated by extraction with ether. Recrystallisation from methanol gave the *enol methyl ether* (VI), m. p. 199—200°, $[\alpha]_D$ +62·7° (*c* 0·75) (Found: C, 69·05, 69·05; H, 8·15, 8·2; OMe, 21·5. $C_{27}H_{36}O_7$ requires C, 68·6; H, 7·7; OMe, 19·7%); $\lambda_{max.}$ 205, 249, and 304 mμ, ε 5,100, 8,540, and 16,100; $\nu_{max.}$ 1742, 1705, 1675, 1621, 1585 cm.$^{-1}$.

The author thanks Dr. F. Sondheimer for a gift of dehydropregnenolone acetate. He is also indebted to Mr. W. McCorkindale for the microanalyses, to Miss N. Caramando for the infrared spectra, and to Mrs. D. Thomson and Miss I. O'Hagan for the ultraviolet spectra.

THE ROYAL COLLEGE OF SCIENCE AND TECHNOLOGY,
GLASGOW, C.1.

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749. *The Cleavage of Diaryl Ethers by Grignard Reagents in the Presence of Cobaltous Chloride. Part III.*[1] *Fluorine-containing Diphenyl Ethers.*

By R. L. HUANG.

THE cleavage of substituted diphenyl ethers by Grignard reagents in the presence of cobaltous chloride, assumed to proceed *via* aryloxy-radicals, enabled a comparison to be made of the relative stabilising influences of substituent groups on such radicals.[1] Conclusions thus reached in general support Ingold's early postulate [2] that electropositivity in substituents stabilises such radicals with respect to hydrogen, but also suggest that

TABLE 1. *Cleavage of* $R{\cdot}C_6H_4{\cdot}O{\cdot}C_6H_4R'$.

R	R′	Ether cleaved (%)	F (%) in phenolic mixture		Mean F (%)	$R{\cdot}C_6H_4{\cdot}OH$ (moles %)
p-F	H	42	9·8	9·8	9·8	54
p-F	*m*-Me	26	3·3	3·2	3·3	20
m-CF_3	H	83	29·0	28·7	28·9	73
m-CF_3	*m*-Me	17	17·0	17·5	17·3	39
m-CF_3	*p*-OMe	14	21·7	22·0	21·9	56

resonance is a more decisive contributing factor toward radical stability. The cleavage of five diphenyl ethers containing the *p*-fluoro- and the *m*-trifluoromethyl substituents is now reported.

Results of fission experiments are summarised in Table 1. If the intermediate formation of aryloxy-radicals is assumed, the cleavage of *p*-fluorophenyl phenyl ether to

[1] Huang, *J.*, 1954, (*a*) (Part I), p. 3084, (*b*) (Part II), p. 3088.
[2] Ingold, *Trans. Faraday Soc.*, 1934, **30**, 52.

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a phenolic mixture containing more than 50 moles % of *p*-fluorophenol indicates that reaction in the main proceeds by way of the *p*-fluorophenoxy-, rather than the phenoxy-, radical, and hence that the former radical is the more stable. Thus in stabilising effect on aryloxy-radicals, *p*-F > H. Similarly, from the direction of cleavage of the other ethers, it would be concluded that: *m*-Me > *p*-F; *m*-CF_3 > H; *m*-Me > *m*-CF_3; and *m*-CF_3 > *p*-OMe. Combining these, we have: *m*-Me > *p*-F > H; and *m*-Me > *m*-CF_3 > *p*-OMe.

In view of the relatively small quantities of ethers used in the cleavage experiments, and of the low percentage reaction in some cases, it is considered that the data obtained give only an indication of the order of stabilising effects.

TABLE 2. *Synthesis of* R·C_6H_4·O·C_6H_4·R′.

R	R′	Phenol, starting material	Yield (%)	B. p./ m.m.	n_D (temp.)	Found (%) C	Found (%) H	Formula	Required C	Required H
p-F	H	Phenol	66	96—98°/2	1·5557 (23°)	76·9	4·85	$C_{12}H_9OF$	76·6	4·8
p-F	*m*-Me	*m*-Cresol	75	81°/0·5	1·5500 (24°)	77·7	5·6	$C_{13}H_{11}OF$	77·2	5·45
m-CF_3	H	Phenol	66	88—89°/2	1·5111 (24°)	65·7	4·1	$C_{13}H_9OF_3$	65·5	3·8
m-CF_3	*m*-Me	*m*-Cresol	30	96—98°/0·5	1·5119 (22°)	66·8	4·5	$C_{14}H_{11}OF_3$	66·7	4·4
m-CF_3	*p*-OMe	*p*-MeO·C_6H_4·OH *	19	90—92°/0·1	1·5188 (23°)	62·6	4·2	$C_{14}H_{11}O_2F_3$	62·7	4·1

* 5 moles used per mole of halide, with 2·5 mols. of potassium hydroxide, the mixture being heated at 180° for 4 hr., 210° for 4 hr., then 230° for another 4 hr.

Experimental.—Synthesis of ethers. The following modification of the Ullmann synthesis was adopted. The phenol (10 mols. per mol. of the halide used), potassium hydroxide (5 mols.) and copper powder were heated in a Pyrex glass tube at 180° under a stream of nitrogen until most of the steam formed had been removed. After addition of the halide the tube was sealed and heated at 180° for 2 hr., then at 240° for 3 hr. The reaction mixture was treated with 10% aqueous sodium hydroxide, and the product isolated by extraction with diethyl ether. The new ethers prepared are listed in Table 2.

p-Bromofluorobenzene was obtained from Light & Co., and *m*-chlorobenzotrifluoride was prepared, in three steps, from benzotrifluoride.[3]

Cleavage experiments. The same procedure as described in Part I was followed, except that a 10 mol. excess of the Grignard reagent and a 5 mol. excess of anhydrous cobaltous chloride were employed. Cleavage was carried out on 2·0—2·5 g. of the ether, except for phenyl *m*-trifluoromethylphenyl ether and *p*-methoxyphenyl *m*-trifluoromethylphenyl ether, of which 4·2 g. and 3·4 g., respectively, were used.

Microanalyses are by Dr. W. Zimmermann, Melbourne.

UNIVERSITY OF MALAYA, SINGAPORE. [*Received, April 14th,* 1958.]

[3] Whalley, *J.*, 1949, 3016.

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750. *Direct Oxidation of Indoles to Oxindoles.*

By C. E. DALGLIESH and W. KELLY.

PERSULPHATE converts indoles and aromatic amines into *O*-sulphates of phenolic derivatives, *e.g.*, indole gives indoxyl *O*-sulphate (indican) and anthranilic acid gives the *O*-sulphates of 3- and 5-hydroxyanthranilic acid.[1] We have found that under the usual, strongly alkaline, conditions skatole is converted into a large number of products, whose properties suggest that in almost all cases the pyrrole ring has opened. Under mildly acid conditions (pH 4—5) a much higher proportion of the products retains the indole nucleus. The major product is 3-methyloxindole.

Skatole is directly oxidised to 3-methyloxindole by peracetic acid,[2] but the yield is low (*ca.* 14%) and the isolation lengthy. Other methods for converting indoles into oxindoles

[1] Boyland, Sims, and Williams, *Biochem. J.*, 1956, **62**, 546.
[2] Witkop, *Annalen*, 1947, **558**, 98.

are: (i) reaction [3] with sulphur monochloride to give the 2 : 2'-disulphide which is then reductively hydrolysed, and (ii) treatment with ferric chloride in the presence of diethylamine to give as one of many products an ether (*e.g.*, 3-methylindol-2-yl 2 : 3-dihydro-3-methylindol-2-yl ether from skatole) which can be split to the substituted indole and substituted oxindole. Overall yields are low in both methods.

In the present simple method the conversion of skatole into 3-methyloxindole was appreciably higher (about 38%). Our interest was in products other than 3-methyloxindole and we have not attempted to find optimal conditions for oxindole formation. The reaction also occurs with 3 : 5-dimethylindole. Indole itself does not give oxindole, but oxidises at the 3-position to give indican (cf. ref. 1).

A possible mechanism of reaction would be formation of the 2-hydroxyindole *O*-sulphate, followed by hydrolysis to the enol form of the oxindole. However, the oxindole is formed, though in lower yield, even at alkaline pH under conditions in which phenolic sulphate esters are usually stable.

Experimental.—The oxidation of skatole to 3-methyloxindole. A solution of potassium persulphate (11·5 g.) and sodium acetate (6 g.) in water (400 ml.) was added to one of skatole (5 g.) in ethanol (250 ml.). The mixture was kept for 2 hr. at room temperature, and then extracted with ether (4 × 300 ml.). The organic solvents were removed, and the residue was again extracted with ether. This second extract was dried and concentrated, and the residue distilled under vacuum (water pump). Unchanged skatole (1·3 g.) was followed by a main fraction, distilling at 175—180° as a yellow syrup which slowly solidified. The product (1·6 g.) was recrystallised from benzene–light petroleum, and then from water. M. p. and mixed m. p. with an authentic sample of 3-methyloxindole were 121—122° (Found: C, 73·4; H, 6·2; N, 9·4. Calc. for C_9H_9ON: C, 73·4; H, 6·2; N, 9·5%). The yield was 28%, or allowing for recovered skatole, 38%.

Oxidation of 3 : 5-dimethylindole. A solution of potassium persulphate (1·10 g.) and sodium acetate (0·6 g.) in water (40 ml.) was added to one of 3 : 5-dimethylindole (0·5 g.) in ethanol (25 ml.) and the mixture kept for 2 hr. at room temperature. Extraction was as for skatole. The residue was fractionally sublimed. Unchanged indole sublimed at 100—110° (water pump) and a yellow gum at 130—140°. The gum was recrystallised from benzene–light petroleum (prisms), then from water (needles), and was then sublimed to give 3 : 5-*dimethyloxindole*, m. p. 154—155° (Found: C, 74·9; H, 7·5. $C_{10}H_{11}ON$ requires C, 74·5; H, 6·9%).

We thank the Medical Research Council for support.

Postgraduate Medical School,
Ducane Road, London, W.12. [*Received, April 22nd,* 1958.]

[3] Wieland, Weiberg, Fischer, and Horlein, *Annalen*, 1954, **587**, 146; Wieland, Weiberg, and Dilger, *ibid.*, 1955, **592**, 69; Freter, Axelrod, and Witkop, *J. Amer. Chem. Soc.*, 1957, **79**, 3191.

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751. *The Chlorination and Bromination of Hydrocarbons under Influence of High-energy Radiation and Other Initiating Agents.*

By R. A. Cox and A. J. Swallow.

It is known that high-energy radiation in common with actinic radiation and free radicals will catalyse the halogenation of organic compounds.[1,2] High-energy radiation interacts with matter to produce in the first instance ions, excited molecules, free radicals, and molecular products from all constituents of a mixture, and it might be expected that the free radicals would initiate the same chain reaction as is produced by other free-radical initiators. On the other hand, because of the unusual nature of the primary act, the

[1] Alyea, *J. Amer. Chem. Soc.*, 1930, **52**, 2743.
[2] Harmer, Martin, and Anderson, *Chem. Eng. Progr. Symp.*, 1954, **50**, 253; *J. Chim. phys.*, 1955, **52**, 666.

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reaction might follow a different course and give products not obtainable by normal means; indeed, previous work [2] had suggested that chlorination induced by γ-rays might follow a different course from the photochemical reaction. We have therefore made a parallel study of radiation- and free-radical-induced chlorination and bromination. Other results of this investigation have been briefly published elsewhere.[3]

Experimental.—Materials. Chlorine was obtained commercially. The first 50% of the gas obtained from the cylinder was discarded to remove any less-dense impurities present initially. The remaining chlorine was passed through calcium chloride and used without further purification. *N*-Bromosuccinimide was recrystallised from hot water and dried under a high vacuum. Its purity determined iodometrically was better than 99%. Nitration-grade toluene was used for the chlorinations. It was fractionally distilled, and the distillate shown to be pure within the limits of gas-phase chromatographic analysis. Benzyl chloride, which was purified by distillation immediately before use, contained traces of benzylidene chloride and chlorotoluene. For the chlorinations " AnalaR " carbon tetrachloride was treated with chlorine, in the absence of oxygen, washed, dried, and distilled before use. *cyclo*Hexene was distilled before use. Other materials were of " AnalaR " quality where possible.

Radiation sources. A " Hanovia " lamp fitted with a glass filter was the source of ultraviolet light. Only wavelengths longer than 3000 Å, and mainly 3660 Å, were emitted. All the incident ultraviolet photons were absorbed in the solution. γ-Irradiations were carried out in a 500-curie cobalt-60 source emitting 1·17 and 1·33 Mev photons, doses being measured with the ferrous sulphate dosimeter, G_{ferric} being assumed [4] to be 15·5. A 2Mev, 0·5 kw Van de Graaff accelerator was used as source of fast electrons. The beam could be scanned over various distances.

Results.—Chlorination. Identical solutions containing an aromatic compound (in excess over chlorine) were prepared for random irradiation with ultraviolet light, γ-rays, or fast electrons, or for thermal reaction in the absence of radiation. All reagents were distilled under a high vacuum into a vessel cooled in liquid nitrogen, and this was allowed to warm to the reaction temperature in the dark. Negligible reaction occurred during the preparation of solutions. Irradiation was continued until all the chlorine had been consumed, solutions being stirred throughout ultraviolet irradiation. The products were then analysed. Hydrogen chloride was measured titrimetrically except when acetic acid was present; it was then measured gravimetrically. Organic products of boiling point below 270° were estimated by gas-phase chromatography. Oily droplets were always found in the reaction vessel. They had the characteristic smell of hexachloro*cyclo*hexane derivatives, and their formation accounts for the excess of chlorine consumed over substitution products formed. Typical results obtained at 18° are shown in the Table. We have also found that at 0° ultraviolet light gives the same distribution of products as γ-rays. From the absorbed dose in the γ-ray experiments the *G*-values were calculated to be of the order of ten thousand, thus proving a chain reaction.

Chlorination of toluene at 18°.
All solutions (10 *ml.*) *contained* 5·5 *mmoles of chlorine initially.*

Solvent	Initiation	Reaction time (min.)	Hydrogen chloride (mmoles)	Benzyl chloride (mmoles)	Chlorotoluene (mmoles)
None	Thermal	720	3·2	0·7	1·6
None	Ultraviolet	0·75	3·8	2·6	0·3
None	γ-Rays	6	3·4	2·9	0·1
None	Fast electrons	<0·02	3·3	3·4	0·2
CCl_4	Ultraviolet	4	4·1	2·5	0
CCl_4	γ-Rays	70	4·3	2·3	0
$CH_3{\cdot}CO_2H$	Ultraviolet	2	3·0	2·7	0·7
$CH_3{\cdot}CO_2H$	γ-Rays	10	3·7	3·0	0·8

In contrast to previous findings [2] we found that benzyl chloride was as readily chlorinated by use of γ-rays as by ultraviolet light, the main products being hydrogen chloride and benzylidene chloride. The chlorination proceeded at about a tenth of the rate of that of toluene. It may be that the lack of chlorination in the previous experiments was due to the

[3] Cox and Swallow, *Chem. and Ind.*, 1956, 1277.
[4] Haybittle, Saunders, and Swallow, *J. Chem. Phys.*, 1956, **25**, 1213.

presence of traces of impurities. Toluene could be chlorinated with γ-rays in benzyl chloride as solvent, the rate being about the same as in acetic acid.

Bromination with N-bromosuccinimide. The best conditions for the radiation-catalysed bromination of *cyclo*hexane were the same as those described by Ford and Waters for chemical catalysis.[5] Bromination was achieved by irradiating a suspension of *N*-bromosuccinimide (10·8 g., 0·06 mole) in boiling *cyclo*hexane (64·7 ml., 0·6 mole) with an electron beam (20 μA), scanned over 20 cm. A product, b. p. 65°/18 mm. (4·4 g.), was shown to be *cyclo*hexyl bromide (46% calculated on the bromo-imide) by conversion into *cyclo*hexylmercuric bromide, m. p. and mixed m. p. 148°. The energy yield was $G = 40$. Higher energy yields could be obtained at lower percentage conversions, but irradiation in the cold or at higher dose rates gave lower energy yields.

*cyclo*Hexene could not be brominated by using radiation under Ford and Waters's conditions because of the rapid occurrence of a dark reaction. However bromination could be achieved in the cold. A suspension of *N*-bromosuccinimide (10·8 g., 0·06 mole) in a mixture of *cyclo*hexene (10·7 ml., 0·106 mole) and carbon tetrachloride (13·3 ml.) was stirred and irradiated in absence of air (20 μA; 20 cm. scan). A product, b. p. 70—72°/30 mm. (6·0 g.), was shown to be 3-bromo*cyclo*hexene (58% calculated on the bromo-imide) by hydrolysis with cold aqueous sodium hydrogencarbonate to *cyclo*hex-2-en-1-ol which in turn was identified bycon version into *cyclo*hex-2-enyl naphthylcarbamate, m. p. and mixed m. p. 156·5°. The energy yield was $G = 450$. Lower yields were obtained at higher dose rates, or when oxygen was present during irradiation, or when carbon tetrachloride was not used.

Discussion.—Our chlorinations show that providing temperature, solvent and concentration of solute are kept the same, there is no significant difference between the products of ultraviolet- and of radiation-catalysed reactions. Moreover, alteration of solvent alters the distribution of products and approximate reaction time equally for the two modes of initiation. Hence the difference between the γ-ray experiments of Harmer, Anderson, and Martin [2] and previous ultraviolet experiments is attributable to differences in reaction conditions. Evidently the propagation steps in the two chain reactions are the same under identical conditions, even though the initial acts differ. The results contrast with the thermal reaction, which gave a different distribution of products. This is probably because the thermal reaction is an ionic one, catalysed by hydrogen chloride,[6] rather than a free-radical chain reaction.

Similarly, when bromination could be carried out under the appropriate conditions, as with *cyclo*hexane, our yields with radiation as catalyst do not differ significantly from those reported by Ford and Waters, using dimethyl αα′-azo*iso*butyrate.[5] Also, in the bromination of toluene previously reported [3] the principal product was benzyl bromide, formed in the same yield as in the reaction catalysed by free radicals. Bromotoluene would have been expected for an ionic reaction.[7]

The authors thank M. Allen and P. J. Horner for technical assistance, W. H. T. Davison and M. McKeown for analyses, and the Chairman of Tube Investments Ltd. for permission to publish this work.

TUBE INVESTMENTS RESEARCH LABORATORIES,
HINXTON HALL, CAMBRIDGE. [*Received, April,* 24th, 1958.]

[5] Ford and Waters, *J.*, 1952, 2240.
[6] Schonken, Le Page, and Jungers, *Bull. Soc. chim. France*, 1957, 1394.
[7] Schmid, *Helv. Chim. Acta*, 1946, **29**, 1144.

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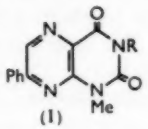
752. *Pteridine Derivatives. Part VI.* Aminolysis of a Pteridone.*

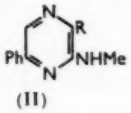
By G. P. G. Dick, D. Livingston, and H. C. S. Wood.

The ease with which *N*-alkylpteridones can be degraded with dilute alkali is well known,[1,2] but the effect of other nucleophilic reagents has not been investigated. Taylor[3] has reported that hydroxypteridines on treatment with a variety of amines undergo cleavage to give *N*-substituted pyrazinecarboxyamides. We now describe briefly the action of amines on 1 : 2 : 3 : 4-tetrahydro-1 : 3-dimethyl-2 : 4-dioxo-7-phenylpteridine (I; R = Me).

It has already been shown[2] that compound (I; R = Me) gives a quantitative yield of 3-methylamino-5-phenylpyrazine-2-carboxymethylamide (II; R = CO·NHMe) when refluxed with ethanolic 0·1N-potassium hydroxide, the initial attack by hydroxyl ion taking place at $C_{(2)}$ and being followed by ring opening. On treatment of the pteridone (I; R = Me) with alcoholic ammonia at 210°, cleavage takes place to give 3-methylamino-5-phenylpyrazine-2-carboxyamide (II; R = CO·NH_2). Similarly the pteridone (I; R = Me) in refluxing hydrazine hydrate gave the carboxyhydrazide (II; R = CO·NH·NH_2). The structure of these degradation products was established in each case by synthesis from the known 3-methylamino-5-phenylpyrazine-2-carboxylic acid (II; R = CO_2H) *via* the methyl ester (II; R = CO_2Me). The initial attack by an amine takes place at $C_{(4)}$ giving the appropriately *N*-substituted pyrazinecarboxyamide directly. The alternative mechanism, which involves attack at $C_{(2)}$ to give the methylamide (II; R = CO·NHMe) followed by aminolysis of the amide group, is excluded by the observation that the methylamide (II; R = CO·NHMe) is not attacked by ammonia under the appropriate conditions.



(I)



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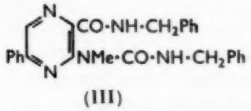

(III)

Benzylamine, which was effective for the cleavage of hydroxypteridines,[3] does not attack the pteridone (I; R = Me) even under drastic conditions. Study of Stuart models indicates that this is probably due to steric hindrance, the methyl group on $N_{(3)}$ preventing the approach of the bulky benzylamine molecule. Support for this suggestion was obtained by treating the pteridone (I; R = H) with benzylamine: cleavage took place to give a pyrazine derivative to which we assign structure (III), analogous to the intermediate compound obtained by Taylor[3] on treatment of a 2 : 4-dihydroxypteridine with benzylamine. None of the expected simple carboxybenzylamide (II; R = CO·NH·CH_2Ph) could be detected in paper chromatograms of the reaction mixture.

The pteridone (I; R = H) was prepared by treatment of the carboxyamide (II; R = CO·NH_2) with ethyl chloroformate to give 2-cyano-3-(*N*-ethoxycarbonyl-*N*-methylamino)-5-phenylpyrazine[4] which readily cyclised to give the pteridone (I; R = H) when refluxed with sodium methoxide.

Experimental.—*3-Methylamino-5-phenylpyrazine-2-carboxyamide.* (*a*) 1 : 2 : 3 : 4-Tetrahydro-1 : 3-dimethyl-2 : 4-dioxo-7-phenylpteridine (0·25 g.), dry ethanol (20 c.c.), and liquid ammonia (5 c.c.) were heated in a steel bomb at 210° for 20 hr. The resulting yellow solution was filtered, and the filtrate evaporated *in vacuo* to an orange-yellow solid. This was extracted

* Part V, *J.*, 1957, 4157.

[1] Albert, Brown, and Wood, *J.*, 1956, 2066; Taylor, *J. Amer. Chem. Soc.*, 1952, **74**, 2380.
[2] Dick, Wood, and Logan, *J.*, 1956, 2131.
[3] Taylor, *J. Amer. Chem. Soc.*, 1952, **74**, 1651.
[4] Cf. Pfleiderer, *Chem. Ber.*, 1956, **89**, 1148.

with boiling light petroleum (b. p. 60—80°; 4 × 30 c.c.), and the combined extracts were evaporated and crystallised from chloroform–light petroleum to give *3-methylamino-5-phenylpyrazine-2-carboxyamide* (0·168 g., 79%) as fine yellow needles, m. p. 188—189° (Found: C, 63·1; H, 4·9; N, 24·7. $C_{12}H_{12}ON_4$ requires C, 63·1; H, 5·3; N, 24·6%).

3-Methylamino-5-phenylpyrazine-2-carboxymethylamide [2] was recovered unchanged when treated with ammonia under the above conditions.

(*b*) Methyl 3-methylamino-5-phenylpyrazine-2-carboxylate (0·13 g.) and saturated ethanolic ammonia (5 c.c.) were heated in a sealed tube at 125° for 5 hr. The cooled mixture was filtered, and the filtrate evaporated to dryness *in vacuo*. The residue, recrystallised from chloroform–light petroleum, gave the carboxyamide (0·1 g., 80%), m. p. and mixed m. p. 188—189°.

3-Methylamino-5-phenylpyrazine-2-carboxyhydrazide. (*a*) The pteridine (I; R = Me) (0·5 g.) and 85% hydrazine hydrate (15 c.c.) were refluxed for 6 hr. The deep yellow needles which separated on cooling were collected, washed with water and methanol, and dried. Recrystallisation from chloroform–methanol gave *3-methylamino-5-phenylpyrazine-2-carboxyhydrazide* (0·37 g., 80%) as fluffy yellow needles, m. p. 215—216·5° (Found: C, 59·3; H, 5·2; N, 28·9. $C_{12}H_{13}ON_5$ requires C, 59·3; H, 5·4; N, 28·8%).

(*b*) Methyl 3-methylamino-5-phenylpyrazine-2-carboxylate (0·1 g.) and 85% hydrazine hydrate (2 c.c.) were refluxed for 30 min., then cooled, and the carboxyhydrazide (0·08 g., 80%) was collected and recrystallised as above (m. p. and mixed m. p. 216—217°).

Methyl 3-methylamino-5-phenylpyrazine-2-carboxylate. 3-Methylamino-5-phenylpyrazine-2-carboxylic acid [2] (85 mg.) in dry boiling methanol (200 c.c.) was treated with dry hydrogen chloride for 10 min., and the solution was refluxed for a further 2 hr. The mixture was concentrated *in vacuo* to 10 c.c., water (10 c.c.) was added, and, on chilling, the *methyl ester* (80 mg., 93%) separated as fine yellow needles, m. p. 134—135° (Found: C, 64·3; H, 5·2; N, 17·3. $C_{13}H_{13}O_2N_3$ requires C, 64·2; H, 5·4; N, 17·3%).

2-Cyano-3-(N-ethoxycarbonyl-N-methylamino)-5-phenylpyrazine. 3-Methylamino-5-phenylpyrazine-2-carboxyamide (1·1 g.) and redistilled ethyl chloroformate (30 c.c.) were refluxed for 20 hr. The solution was evaporated to dryness *in vacuo*, ethanol (50 c.c.) was added, and the solution again taken to dryness. Extraction of the residue with light petroleum (b. p. 60—80°; 50 c.c.), and refrigeration of the extract gave the *nitrile* (1·02 g., 75%) as thick colourless blades, m. p. 66—67° (Found: C, 63·9; H, 4·5; N, 20·0. $C_{15}H_{14}O_2N_4$ requires C, 63·8; H, 5·0; N, 19·9%). The infrared spectrum (in CCl_4) shows bands at 2247 (CN) and 1739 cm.$^{-1}$ (ester).

1 : 2 : 3 : 4-Tetrahydro-1-methyl-2 : 4-dioxo-7-phenylpteridine. The above nitrile (0·64 g.) in methanol (10 c.c.) was added to a solution from sodium (0·5 g.) in methanol (20 c.c.), and the mixture was heated on the steam-bath for 1 hr. The resulting solution was taken to dryness *in vacuo*, water (25 c.c.) was added, and the pH was adjusted to *ca.* 4 with dilute hydrochloric acid. The pale yellow solid which separated was collected and recrystallised from 80% formic acid, to give the *pteridone* (0·23 g., 34%) as yellow needles, m. p. 349—350° (Found: C, 61·3; H, 3·5; N, 21·8. $C_{13}H_{10}O_2N_4$ requires C, 61·4; H, 4·0; N, 22·0%).

3-(N-Benzylcarbamoyl-N-methylamino)-5-phenylpyrazine-2-carboxybenzylamide. The pteridone (0·15 g.) was refluxed for 8 hr. with redistilled benzylamine (3 c.c.). On cooling, fine yellow needles (50 mg.) separated which recrystallised readily from benzylamine, to give *3-(N-benzylcarbamoyl-N-methylamino)-5-phenylpyrazine-2-carboxybenzylamide*, m. p. 255—256° (Found: C, 71·7; H, 4·8. $C_{27}H_{23}O_2N_5$ requires C, 71·8; H, 5·5%). The infrared spectrum (in $CHCl_3$) shows a strong carbonyl absorption band at 1660 and a medium band at 1700 cm.$^{-1}$ (cf. ref. 3).

3-Methylamino-5-phenylpyrazine-2-carboxybenzylamide. Methyl 3-methylamino-5-phenylpyrazine-2-carboxylate (0·22 g.) and benzylamine (5 c.c.) were refluxed together for 30 min. The solution was taken to dryness *in vacuo*, and re-evaporated several times with ethanol to remove traces of benzylamine. Crystallisation of the residue from aqueous methanol gave the *benzylamide* (0·15 g., 52%) as yellow needles, m. p. 96—97° (Found: C, 71·8; H, 5·7; N, 17·6. $C_{19}H_{18}ON_4$ requires C, 71·7; H, 5·7; N, 17·6%).

THE ROYAL COLLEGE OF SCIENCE AND TECHNOLOGY,
GLASGOW.

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753. *The Vapour Density and Dissociation Pressure of Phosphorus Pentabromide.*

By G. S. Harris and D. S. Payne.

There is no record of the vapour density of phosphorus pentabromide though, in text-books, it is generally assumed that the vapour is more or less dissociated into phosphorus tribromide and bromine: $PBr_5 \rightleftharpoons PBr_3 + Br_2$. To obtain information about the extent of dissociation, vapour density was measured over a wide temperature range (65—180°). The apparent molecular weight of the vapour remains constant, within experimental error, at half the calculated molecular weight of phosphorus pentabromide, corresponding to complete dissociation.

The dissociation pressure of solid phosphorus pentabromide was also re-measured (from 19·0° to 75·0°) (data were reported by Prideaux [1] and van Driel and Gerding [2]). The plot of $\log_{10} p$ (mm.) *versus* $1/T°$ (abs.) in the range 32·5—75·0° was reproducibly straight and described by $\log_{10} p = -2895{\cdot}7T^{-1} + 10{\cdot}1713$ (by the method of least squares). From this and the complete dissociation of the vapour at 65·0°, it follows that between 32·5° and 75° the solid-vapour equilibrium is of the type Solid $\rightleftharpoons$ Gas + Gas for which the equilibrium constant (K_P) is $K_P = \frac{1}{4}P^2$ [P is the total pressure, atm.). Consequently, for phosphorus pentabromide, $\log_{10} K_P$ (atm.) $= 5791{\cdot}4T^{-1} + 13{\cdot}979$ which gives 26·50 kcal. mole^{-1} as the heat of dissociation of solid phosphorus pentabromide to gaseous phosphorus tribromide and bromine (van Driel and Gerding's data yield a value of 27·12 kcal. mole^{-1}). From 19·0° to 32·5° the vapour pressures tended upward, possibly owing to incomplete dissociation of the vapour at these lower temperatures. Vapour density was not measured in this range because of the reduced sensitivity of the method at very low pressures.

Experimental.—Good commercial phosphorus pentabromide was recrystallised from pure nitrobenzene and washed with dry ether, the last traces of which were removed in a current of dry nitrogen. The compound was manipulated in a dry-box.

Dissociation pressures. These were measured by a static method in an all-glass system incorporating a spoon-gauge with an optical lever which was used as a null-meter. Pressures were read on a cathetometer as a difference in mercury levels in a wide-tube manometer.

The constant-volume section of the apparatus (containing the compound) was kept at constant temperature in an electrically heated oil-bath. The dissociation pressure was recorded only after solid–vapour equilibrium was set up (after 1—2 hr.); values for ascending and descending temperatures are grouped together in Table 1. The mean deviation of values of $\log_{10} p$ is 0·017318.

Table 1. *Dissociation pressure of solid phosphorus pentabromide.*

Temp. (° c)	76·0	72·9	65·2	65·1	61·8	61·0	59·9	57·9	57·5	55·8	55·0
P (mm.) ...	75·85	68·16	43·14	38·90	34·00	30·45	26·70	26·57	26·06	23·29	22·99
Temp. (° c)	52·0	49·0	49·0	48·0	44·4	41·9	40·7	39·0	36·0	35·1	32·4
P (mm.) ...	18·19	13·09	14·94	14·29	10·97	9·72	8·26	7·80	6·06	6·30	5·30

Vapour density. A similar apparatus was used, but the constant-volume part was enlarged by the attachment of a bulb (*ca.* 100 ml.). Small samples of the compound were used so that it would vaporise completely. The temperature of the thermostat was raised in stages and the corresponding pressures noted. The temperature at which complete vaporisation occurred was observed visually and from the abrupt levelling-off of the pressure–temperature graph. Beyond this point and up to 180° the pressure at various temperatures was recorded and in this region the P–T graph was straight with a small positive slope. From these measurements and the mass and volume of vapour, the apparent molecular weight M (app.) (calc. for PBr_5: M, 430·6), and hence the degree of dissociation (α) of phosphorus pentabromide were calculated.

[1] Prideaux, *J.*, 1909, **95**, 445.
[2] van Driel and Gerding, *Rec. Trav. chim.*, 1941, **60**, 869.

Table 2 summarises the results of two experiments with 0·0595 g. and 0·1697 g. samples of phosphorus pentabromide in volumes of 144·8 ml. and 143·4 ml. respectively. The estimated error is about 1%.

TABLE 2. *State of phosphorus pentabromide vapour.*

Temp. (° c) ...	65·0	77·5	90·0	100·0	110·0	122·5	137·5	150·0	165·0	180·0
P (mm.)	40·0	41·5	43·1	44·4	131·5	135·9	141·1	145·3	150·2	155·1
M (app.)	216·9	216·8	216·1	215·7	215·1	214·9	214·9	215·0	215·4	215·7
α (%)	98·5	98·6	99·2	99·6	100·2	100·3	100·4	100·2	99·9	99·6

We thank the Department of Scientific and Industrial Research for an award (to G. S. H.).

THE UNIVERSITY, GLASGOW, W.2. [*Received, April 28th*, 1958.]

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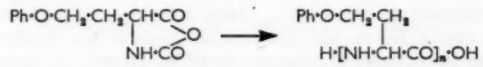
754. *Synthesis of Poly-O-phenyl-DL-homoserine.*

By MAX FRANKEL and Y. KNOBLER.

N-CARBOXY-*O*-PHENYL-DL-HOMOSERINE ANHYDRIDE, m. p. 105°, has been prepared by us from the benzyloxycarbonyl derivative of *O*-phenyl-DL-homoserine[1] or, preferably, directly[2] from the amino-acid and carbonyl chloride. Polymerisation of the *N*-carboxy-anhydride was effected by melting it under a vacuum.



The hard brittle polymers obtained were soluble in dimethylformamide or in chloroform and precipitated on addition of ether. Glacial acetic acid caused partial dissolution, leaving the higher-melting fractions of greater chain-length undissolved; from the soluble, lower-melting fractions, polymers of shorter chain-length were recovered on precipitation with water.

The poly-*O*-phenyl-DL-homoserine preparations obtained from the *N*-carboxy-anhydride synthesised by action of carbonyl chloride on the free amino-acid had greater average chain-length, as shown by their amino-nitrogen content. They exhibited pronounced fibre-forming properties. The fractions not soluble in hot glacial acetic acid had the greatest ability of extension on stretching. Fractions of an average molecular weight of 21,000—26,000, corresponding to an average chain-length of 120—150 units, were obtained.

Experimental.—M. p.s were determined in a Fisher–Johns apparatus.

N-*Benzyloxycarbonyl*-O-*phenyl*-DL-*homoserine*. Benzyl chloroformate (7·3 g.) and 4N-sodium hydroxide (15 ml.) were dropped with stirring simultaneously into a solution of *O*-phenyl-DL-homoserine (7·8 g.) in 2N-sodium hydroxide (30 ml.) at 0° during ½ hr.; stirring was continued for ½ hr. at 0° and for 1 hr. without cooling. Washing the mixture with toluene and precipitation with 18% hydrochloric acid gave an oil which solidified at 0°. The solid recrystallised from ether–light petroleum or ethyl acetate–light petroleum, giving *N*-benzyloxycarbonyl-*O*-phenyl-DL-homoserine (9·2 g., 70%), m. p. 118° (Found: C, 65·4; H, 5·7; N, 4·25. $C_{18}H_{19}O_5N$ requires C, 65·6; H, 5·8; N, 4·25%).

N-*Carboxy*-O-*phenyl*-DL-*homoserine anhydride*. (*a*) *N*-Benzyloxycarbonyl-*O*-phenyl-DL-homoserine (6·6 g.) was dissolved in dry ether (200 ml.) and treated with phosphorus pentachloride (4·1 g.) in the usual manner. The anhydride solidified under light petroleum or over phosphoric oxide. Recrystallised from ether–light petroleum, dioxan–light petroleum, or ethyl acetate–light petroleum it gave the *N-carboxy-anhydride* (3·6 g., 81%) as a white powder, m. p. 105°. It decomposes slowly in cold water; a ninhydrin reaction is detectable only after boiling. After prolonged storage in water it gave a gradually deepening biuret colour, positive

[1] Fischer and Blumenthal, *Ber.*, 1907, **40**, 106; Painter, *J. Amer. Chem. Soc.*, 1947, **69**, 232.
[2] Fuchs, *Ber.*, 1922, **55**, 2943; Levy, *Nature*, 1950, **165**, 152; Farthing and Reynolds, *Nature*, 1950, **165**, 647.

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also in pyridine solution [Found: C, 60·0; H, 5·2; N (Kjeldahl), 6·1; N (Van Slyke), 6·2. $C_{11}H_{11}O_4N$ requires C, 59·7; H, 5·0; N, 6·3%].

(*b*) The *N*-carboxy-anhydride was prepared by passing dry carbonyl chloride at 40—60° (bath) through a suspension of *O*-phenyl-DL-homoserine (3·9 g.) in dioxan. Recrystallised as under (*a*), the anhydride (3 g., 70%) had m. p. 105—106°. It evolved carbon dioxide when heated in water, giving then a positive ninhydrin and a slight biuret reaction (positive biuret reaction in pyridine solution) [Found: C, 59·6; H, 5·1; N (Kjeldahl), 6·2; N (Van Slyke), 6·2%].

Poly-O-phenyl-DL-homoserine. Freshly prepared recrystallised *N*-carboxy-anhydride (4·6 g.) was gradually heated at an initial pressure of 0·5—1 mm. At 100—110° (bath) the substance melted with evolution of gas, causing rise in pressure. The bath temperature was kept during 1 hr. at 100—110°, then raised during 2 hr. to 135°, causing steady evolution of gas and finally vigorous foaming. As no gas evolution occurred by increasing the bath temperature at this point, the substance was kept for 1 hr. at 100° (bath) at the initial pressure.

Poly-*O*-phenyl-DL-homoserine, synthesised from the anhydride obtained by method (*b*), was washed with hot (100°) glacial acetic acid and subsequently with dry ether. Dried over phosphoric oxide *in vacuo* it became plastic at 260—280° and decomposed at 280—300°. After evaporation of its chloroform solution, the soft mass remaining could be cold drawn to form elastic fibres, which on loss of solvent became rigid. The average chain-length of this fraction varied between 120 and 150 units [Found: C, 67·6; H, 6·3; N (Kjeldahl), 7·9; N (Van Slyke), 0·065, 0·06, 0·05, 0·05. $(C_{10}H_{11}O_3N)_{120}$ requires C, 67·7; H, 6·2; N, 7·9; N (amino), 0·66. $(C_{10}H_{11}O_3N)_{150}$ requires N (amino), 0·053%].

The fraction precipitated from chloroform–ether and dried *in vacuo* (P_2O_5) became plastic at 225—250° and decomposed at 250—280°. After softening with chloroform it also could be cold drawn to form elastic fibres, but less readily than in the former case. Its average chain-length varied from 40 to 70 units [Found: C, 67·3; H, 6·1; N (Kjeldahl), 7·9; N (Van Slyke), 0·2, 0·15, 0·15, 0·11. $(C_{10}H_{11}O_3N)_{50}$ requires N (amino), 0·16%].

Poly-*O*-phenyl-DL-homoserine obtained by heating *in vacuo* (as above) of the anhydride prepared *via* the chloride of the *N*-benzyloxycarbonyl-acid had shorter average chain-length after undergoing the same fractionation. The fraction insoluble in glacial acetic acid (100°) was a polymer of 20—30 units, semiplastic at 150—200°, melting at 200—230°, decomposing above 250°. It softened after addition of chloroform; its ability to be stretched was very limited [Found: C, 66·5; H, 6·0; N (Kjeldahl), 7·6; N (Van Slyke), 0·3, 0·3, 0·5. $(C_{10}H_{11}O_3N)_{20}$ requires N (amino), 0·4%). Substances precipitated from dimethylformamide–ether or from chloroform–ether were of an average chain-length 10—20 units; the fraction soluble in glacial acetic acid and precipitated with water was composed (average) of 10 units, having lower melting ranges and without fibre-forming properties.

All fractions (2—2·5 g.) gave an intensive biuret colour.

DEPARTMENT OF ORGANIC CHEMISTRY, THE HEBREW UNIVERSITY,
JERUSALEM, ISRAEL.

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755. *The Heat of Formation of Trimethylgallium.*

By P. A. FOWELL and C. T. MORTIMER.

THE thermochemistry of alkyl and aryl compounds of the Group II metals zinc, cadmium, and mercury has been studied in some detail and information is also available for the alkyl compounds of the Group IV metals tin and lead.[1] Comparatively little is known about the metal–carbon bond in the alkyls of the Group III metals gallium, indium, and thallium. The heat of reaction at 55° of liquid trimethylgallium with iodine in benzene solution, which has now been measured, yields $\Delta H_f°(GaMe_3, liq.) = -14·5 \pm 8$ kcal./mole. The *mean* dissociation energy of the Ga–C bond in trimethylgallium is $56·7 \pm 4$ kcal./mole.

Experimental.—Materials. Trimethylgallium was prepared by refluxing, under nitrogen, gallium (Light and Co., 99·95% pure), dimethylmercury (b. p. 91·0—91·2°/748 mm.), and a

[1] For references, see Mortimer, *J. Chem. Educ.*, 1958, in the press.

trace of methylmercury chloride as catalyst.[2] After 24 hr. the vapour temperature fell and trimethylgallium (4 g.) was taken from the top of a 6 in. Fenske column during 24 hr. (b. p. 56·0°/764 mm.; Kraus and Toonder [3] give 55·7 ± 0·2°/762 mm.). It was redistilled *in vacuo* and sealed in thin, weighed glass phials.

Gallium tri-iodide (Johnson Matthey and Co.), analysed by the 8-hydroxyquinoline method,[4] was 99·9% pure.

Iodine and benzene were " AnalaR "; the latter was washed four times with concentrated sulphuric acid, then with sodium hydrogen carbonate, and dried by refluxing it with calcium hydride in a stream of nitrogen (trimethylgallium reacts vigorously with both oxygen and water).

Methyl iodide was distilled through an 18 in. Fenske column, and redistilled *in vacuo* before use.

Calorimeter. This was a narrow-necked 400 ml. Dewar vessel, immersed in an oil-bath at 60°, and contained 350 ml. of Shell Diala BX oil, initially at 55°. The oil covered a stirrer (480 r.p.m.), a shielded thermistor, a calibration heater, and a reaction vessel. The last contained 25 ml. of a solution of iodine in benzene, saturated with nitrogen, and a phial of trimethylgallium which was broken to start the reaction. The usual temperature rise was about 0·25°. The energy equivalent of the calorimeter was determined electrically by substitution.

Units. All heat quantities are given in units of the thermochemical calorie, 1 cal. ≡ 4·1840 abs. joule. The reactions were carried out at 55°.

Results. According to Wiberg, Johannsen, and Stecher [5] the reaction

$$GaMe_3,liq. + 3I_2,c. \longrightarrow GaI_3,c. + 3MeI,liq. \quad . \quad . \quad . \quad . \quad . \quad (1)$$

proceeds slowly, but quantitatively, at room temperature, and more quickly at 60°. At room temperature, both in benzene and ether, only two-thirds of the theoretical quantity of iodine reacted immediately:

$$GaMe_3,liq. + 2I_2,soln. \longrightarrow MeGaI_2,soln. + 2MeI,soln. \quad . \quad . \quad . \quad . \quad (2)$$

At 55° in benzene, with a molar ratio of trimethylgallium to iodine of 1 : 7, about 70% of the iodine required by eqn. (1) reacted, and with a ratio of 1 : 20 the amount was 87%. Of the total heat of reaction, about 80% was evolved in the first 4 min., and after 45 min., heat continued to be evolved at the rate of 0·3% per min. The temperature of the contents of the calorimeter at this time was arranged to be near the " equilibrium " temperature, so that heat transfer was small. About 45 min. after the reaction had started, the reaction vessel was removed from the calorimeter and cooled, and the contents were analysed for iodine. It was estimated that the error in the measurement of the heat of reaction was not more than ±0·5 kcal./mole and that in determining the percentage of reaction ±1%.

To produce a high percentage of reaction required a large excess of iodine, which, however, has a comparatively low solubility (~0·6M) in benzene. Thus, high percentages could only be achieved by using small amounts of trimethylgallium, with consequently small temperature changes. Attempts to increase the temperature change by using more benzene involved the difficulties of stirring a closed system at 55° or of keeping an open system free from oxygen and moisture, and the errors introduced outweighed the advantage.

The observed heats of reaction, $\Delta H_{obs.}$, in benzene, together with the amount of iodine consumed as a percentage of that required by reaction (1), are tabulated. A plot of $\Delta H_{obs.}$

$GaMe_3$ (g.)	0·3383	0·1052	0·1262	0·0529	0·0950	0·1178	0·0488	0·0877
Iodine consumed (%)	70·7	71·4	72·6	78·0	80·6	82·5	86·6	87·0
$-\Delta H_{obs.}$ (kcal./mole)	48·5	47·5	49·1	50·9	54·4	54·0	53·5	57·3

against iodine consumed (%), when extrapolated to 66·7% of iodine consumed, gives $\Delta H_{(2)} = -46·4 \pm 1$ kcal./mole for the heat of reaction (2) and to 100% of iodine consumed gives $\Delta H_{(3)} = -60·5 \pm 2$ kcal./mole for the heat of the reaction

$$GaMe_3,liq. + 3I_2,soln. \longrightarrow GaI_3,soln. + 3MeI,soln. \quad . \quad . \quad . \quad . \quad (3)$$

[2] Coates, *J.*, 1951, 2003.
[3] Kraus and Toonder, *Proc. Nat. Acad. Sci. U.S.A.*, 1933, **19**, 292.
[4] Moeller and Cohen, *Analyt. Chem.*, 1950, **22**, 686.
[5] Wiberg, Johannsen, and Stecher, *Z. anorg. Chem.*, 1943, **251**, 114.

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There was no heat change when a phial containing liquid methyl iodide was broken in iodine–benzene at 55°. Gallium tri-iodide dissolved slowly in benzene containing both dissolved iodine and methyl iodide with no measurable heat change. The heat of solution in benzene [6]

$$I_2,c. \longrightarrow I_2,soln.\ \Delta H_{I_2,soln.} = +4{\cdot}25 \text{ kcal./mole at } 25°$$

gives $$\Delta H_{(1)} = \Delta H_{(3)} + 3\Delta H_{I_2,soln.} = -47{\cdot}8 \pm 2 \text{ kcal./mole}$$

The heat change when methylgallium di-iodide dissolves in benzene containing dissolved iodine and methyl iodide was not measured. However, if it is zero, as for gallium tri-iodide, then the heat, $\Delta H_{(4)}$, of the reaction

$$GaMe_3,liq. + 2I_2,c. \longrightarrow MeGaI_2,c. + 2MeI,liq. \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

given by $\Delta H_{(4)} = \Delta H_{(2)} + 2\Delta H_{I_2,soln.}$ is $-37{\cdot}9 \pm 1$ kcal./mole.

Discussion.—The heats of formation of liquid trimethylgallium and crystalline methylgallium di-iodide can be calculated from the $\Delta H_{(1)}$ and $\Delta H_{(4)}$ by incorporating $\Delta H_f°(GaI_3,c.) = -51{\cdot}2$ kcal./mole [7] and $\Delta H_f°(MeI,liq.) = -3{\cdot}7 \pm 2$ kcal./mole (values of the heat of formation of methyl iodide have been critically considered by Hartley, Pritchard, and Skinner,[8] and Skinner [9] has suggested that this value is the " best ").

Too few specific-heat data are available to calculate $\Delta H_{(1)}$ and $\Delta H_{(4)}$ at 25° from the value at 55°. However, assuming these to be the same at 25°, we calculate $\Delta H_f°(GaMe_3,liq.) = -14{\cdot}5 \pm 8$ kcal./mole, and incorporating the heat of vaporisation, $\Delta H_{vap.} = 7{\cdot}8$ kcal./mole,[3] we find $\Delta H_f°(GaMe_3,g.) = -6{\cdot}7 \pm 8$ kcal./mole.

Taking our value for $\Delta H_f°(GaMe_3,liq.)$ and that already given for $\Delta H_f°(MeI,liq.)$, we find $\Delta H_f°(MeGaI_2,c.) = -45{\cdot}0 \pm 5$ kcal./mole.

The *mean* bond dissociation energy $\bar{D}(Ga–C)$, for the dissociation

$$GaMe_3,g \div Ga,g. + 3Me,g.$$

can be calculated from the relation

$$3\bar{D}(Ga–C) = \Delta H_f°(Ga,g.) + 3\Delta H_f°(Me,g.) - \Delta H_f°(GaMe_3,g.)$$

Using our value for $\Delta H_f°(GaMe_3,g.)$, together with $\Delta H_f°(Me,g.) = 32{\cdot}6 \pm 1$ kcal./mole [10] and $\Delta H_f°(Ga,g.) = 65{\cdot}6 \pm 0{\cdot}5$ kcal./mole,[11] we find $\bar{D}(Ga–C) = 56{\cdot}7 \pm 4$ kcal./mole.

The authors thank Dr. H. A. Skinner for advice. One of them (P. A. F.) thanks the Distillers Co. Ltd. for a maintenance grant.

UNIVERSITY COLLEGE OF NORTH STAFFORDSHIRE. [*Received, April 29th*, 1958.]

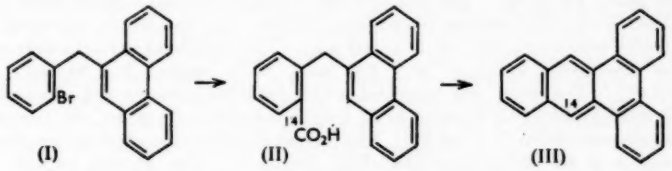
[6] Hartley and Skinner, *Trans. Faraday Soc.*, 1950, **46**, 621.
[7] Klemm, Tilk, and Jacobi, *Z. anorg. Chem.*, 1932, **207**, 187.
[8] Hartley, Pritchard, and Skinner, *Trans. Faraday Soc.*, 1950, **46**, 1019.
[9] Skinner, personal communication.
[10] Mortimer, Pritchard, and Skinner, *Trans. Faraday Soc.*, 1952, **48**, 220
[11] Speiser and Johnson, *J. Amer. Chem. Soc.*, 1953, **75**, 1469.

756. ^{14}C-*Labelled Polycyclic Aromatic Hydrocarbons. Part IV.*[1] *A Synthesis of* 1 : 2-3 : 4-*Dibenz*[9-^{14}C]*anthracene and the Attempted Synthesis of* 1 : 2-3 : 4-5 : 6-*Tribenzanthracene.*

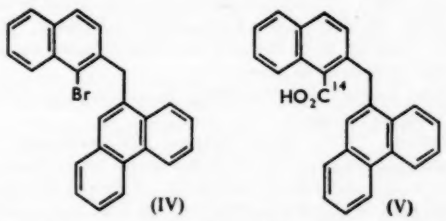
By E. A. Evans.

In continuation of the investigation of new improved synthetic routes to ^{14}C-labelled polycyclic aromatic hydrocarbons,[2] this Note records the synthesis, from $^{14}CO_2$ in three steps only, of the pentacyclic weakly carcinogenic hydrocarbon 1 : 2-3 : 4-dibenz[9-^{14}C]-anthracene.[3] An unsuccessful attempt to prepare 1 : 2-3 : 4-5 : 6-tribenzanthracene[4] is also recorded.

The route chosen was similar to that described in previous papers in this series.[2] The intermediate bromide (I) was prepared by reaction of *o*-bromobenzaldehyde with 9-phenanthrylmagnesium bromide, followed by reduction of the secondary alcohol with red phosphorus and iodine in glacial acetic acid. In a Grignard reaction with $^{14}CO_2$ the



bromide (I) gave 75—98% yields of the acid (II), identical with that prepared by Clemmensen reduction of 9-*o*-carboxybenzoylphenanthrene[5] made from 9-phenanthrylmagnesium bromide and phthalic anhydride. Attempts to cyclise 9-*o*-carboxybenzoylphenanthrene with concentrated sulphuric acid or with phosphoric oxide in tetralin gave unidentifiable brown amorphous solids, even under mild conditions.[6] However, the acid (II) was readily cyclised in hydrogen fluoride and was then reduced to the hydrocarbon (III) with zinc dust in sodium hydroxide. The overall yield from $^{14}CO_2$ was approximately 30%.



The dibenzanthracene was best purified by crystallisation from glacial acetic acid and, as in the case of 1 : 2-5 : 6-dibenzanthracene,[1] only partial purification could be effected by chromatography on alumina in benzene. The radiochemical purity determined by dilution analysis was greater than 98%.

An attempt to prepare the bromo-compound (IV) by reaction of 1-bromo-2-naphthaldehyde with 9-phenanthrylmagnesium bromide followed by reduction of the

[1] Part III, *J.*, 1957, 2796.
[2] Catch and Evans, *J.*, 1957, 2796, and preceding papers.
[3] Cf. Elsevier's "Encyclopaedia of Organic Chemistry," Vol. XIV, p. 450; Clar and Lombardi, *Ber.*, 1932, **65**, 1411.
[4] Fieser and Dietz, *Ber.*, 1929, **62**, 1827.
[5] Bergmann and Berlin, *J.*, 1939, 493.
[6] Cf. Graebe and Peter, *Annalen*, 1905, **340**, 259; Weizmann, Bergmann, and Bergmann, *J.*, 1935, 1367.

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alcohol gave a bromo-compound containing approximately 50% of the expected bromine content. The compound formed a Grignard reagent with difficulty, and on carboxylation gave a poor yield of the acid (V) (?). Attempted cyclisation of this acid (V) with anhydrous hydrogen fluoride, followed by reduction with zinc dust in 5N-sodium hydroxide, gave only traces of unidentifiable brown solids.

Experimental.—M. p.s were observed on a Kofler block and are corrected. Ultraviolet absorption measurements were made on ethanol solution by a Unicam S.P. 500 instrument. Grignard reactions were conducted in dry oxygen-free nitrogen.

9-o-*Bromobenzylphenanthrene.* *o*-Bromobenzaldehyde (9 g.) in anhydrous ether (25 ml.) was added dropwise to 9-phenanthrylmagnesium bromide (prepared from 9-bromophenanthrene 13 g., magnesium 1·5 g., and iodine one crystal) in ether (20 ml.) and benzene (20 ml.). After 1 hour's stirring of the mixture at room temperature excess of saturated aqueous ammonium chloride was added and the ether–benzene layer separated. The aqueous layer was extracted with ether (2 × 20 ml.), the organic layers were combined, and the solvents removed under reduced pressure. The residual dark brown oil was dissolved in glacial acetic acid (150 ml.), then iodine (3 g.), red phosphorus (3 g.), and water (15 ml.) were added and the mixture was heated under reflux for 27 hr. The solution was cooled to 0° and filtered, most of the acetic acid neutralised with 10% sodium hydroxide solution, and the whole extracted with ether until the extracts were colourless (*ca.* 3 × 100 ml.). The combined extracts were washed with 10% sodium hydroxide solution (2 × 100 ml.), then water (2 × 50 ml.), and dried (Na_2SO_4–Na_2CO_3). The ether was removed under reduced pressure and the residual brown solid was chromatographed on alumina in 3 : 1 light petroleum (b. p. 40—60°)–benzene, giving 9-o-*bromobenzylphenanthrene* (7 g., 41·5%), which crystallised in colourless plates [from benzene–light petroleum (b. p. 40—60°)], m. p. 134—135° (Found: C, 72·8; H, 4·6; Br, 22·1. $C_{21}H_{15}Br$ requires C, 72·7; H, 4·3; Br, 23·0%).

9-o-[^{14}C]*Carboxybenzylphenanthrene.* A Grignard reagent was prepared from 9-*o*-bromobenzylphenanthrene (3·5 g.), magnesium (0·25 g.), iodine (1 crystal), and methyl iodide (1—2 drops) in ether (15 ml.) and benzene (15 ml.) under reflux in 2—3 hr. $^{14}CO_2$ (generated from barium [^{14}C]carbonate, 1·773 g., 0·9 mc, with concentrated sulphuric acid) was condensed into the above Grignard reagent in a closed vacuum-system by freezing in liquid nitrogen. The solution was stirred for 30 min. at room temperature and the acid isolated with ether. The ether was extracted with 2N-sodium hydroxide (*ca.* 5 × 20 ml.), and the combined alkaline extracts on acidification at 0° with concentrated hydrochloric acid gave the carboxylic acid (2·128 g., 76%), m. p. 188—190°. This crystallised in plates (from benzene–*cyclo*hexane), m. p. 189—190° (Found: C, 85·0; H, 5·1. Calc. for $C_{22}H_{16}O_2$: C, 84·6; H, 5·1%) (Bergmann and Berlin [8] give m. p. 197°). The m. p. of the acid was undepressed on admixture with the acid, m. p. and mixed m. p. 189°, prepared as below.

In other carboxylations, yields from 75 to 98% (based on CO_2) of the acid were obtained by increasing the excess of Grignard reagent.

High-activity preparation. $^{14}CO_2$ (from barium [^{14}C]carbonate, 0·394 g., 20 mc) was condensed into a Grignard reagent prepared from 9-*o*-bromobenzylphenanthrene (1 g.), magnesium (0·1 g.), iodine (1 crystal), and methyl iodide (1—2 drops) in ether (15 ml.) and benzene (10 ml.). Isolation of the acid as above gave the [^{14}C]oic acid (0·5 g., 80%), m. p. 188—190°.

1 : 2-3 : 4-*Dibenz*[9-^{14}C]*anthracene.* The acid (2·128 g., *ca.* 100 μc/mmole) was left in anhydrous hydrogen fluoride (20—25 ml.) for 1 hr. at room temperature with frequent stirring, and then poured on ice. The product was filtered off and heated under reflux for 10 hr. with zinc dust (15 g., previously activated with copper sulphate solution), 5N-sodium hydroxide (100 ml.), and toluene (50 ml.). After cooling, the toluene layer was separated and the aqueous layer extracted with benzene (2 × 50 ml.). The excess of zinc dust was washed with hot benzene (3 × 10 ml.), and the combined benzene and toluene layers were dried (Na_2SO_4). Organic solvents were distilled off under reduced pressure, leaving a yellow solid which crystallised in straw-coloured needles (0·8 g., 42%) (from glacial acetic acid), m. p. 199—201°. (Clar and Lombardi [3] give m. p. 205°.)

The specific activity of the hydrocarbon was 92·4 μc/mmole of radiochemical purity 99% (by dilution analysis, see Part III), and the overall radiochemical yield from $^{14}CO_2$ was 29%. Only traces of acid were recovered from the alkaline liquors of the reduction.

In the high-activity preparation on a 2-mmolar scale, carrier dibenzanthracene was added

before the material was purified. From acid (0·5 g., *ca.* 16 mc) was obtained 1 : 2-3 : 4-dibenz[9-^{14}C]anthracene (2·87 mc) at 2·79 mc/mmole. The radiochemical purity was found to be 98% by dilution analysis.

9-*o*-*Carboxybenzoylphenanthrene*. 9-Phenanthrylmagnesium bromide (prepared from 9-bromophenanthrene 14 g., magnesium 1·5 g., and iodine 1 crystal) in ether (20 ml.) and benzene (30 ml.) was added dropwise to phthalic anhydride (7 g.) in benzene (200 ml.). A canary-yellow complex was formed and the mixture was heated under reflux for 2 hr. The solution was cooled and poured into excess of ice-cold 2N-sulphuric acid. The organic layer was separated, the aqueous layer was extracted with 2N-sodium carbonate (5 × 50 ml.), and the alkaline extracts were acidified with concentrated hydrochloric acid. The acid (15 g.) was filtered off, dried in *vacuo*, and crystallised from xylene or benzene–*cyclo*hexane in plates, m. p. 176—177° (Weizmann, Bergmann, and Bergmann [6] give m. p. 174—175°). Lower yields of the acid were obtained when the phthalic anhydride was added to the Grignard reagent.

Amalgamated zinc was prepared by shaking for 5 min. a mixture of zinc wool (50 g.), mercuric chloride (5 g.), water (150 ml.), and concentrated hydrochloric acid (5 ml.). The solution was decanted and the following added to the zinc: water (50 ml.), concentrated hydrochloric acid (120 ml.), toluene (100 ml.), and 9-*o*-carboxybenzoylphenanthrene (5 g.). The solution was heated under reflux for 30 hr. and concentrated hydrochloric acid (30 ml.) was added every 6 hr. for the first 18 hr. After cooling, the toluene layer was separated and the aqueous layer extracted with ether (3 × 50 ml.), the zinc being washed each time. The combined organic layers were extracted with 2N-sodium hydroxide (5 × 20 ml.), and the acid was precipitated from the alkaline extracts with concentrated hydrochloric acid at 0°. Crystallisation from benzene–*cyclo*hexane gave plates (3 g.), m. p. 189—190°, undepressed on admixture with the 9-*o*-carboxybenzylphenanthrene prepared as above.

Carrier 1 : 2-3 : 4-*dibenzanthracene*. Cyclisation of 9-*o*-carboxybenzylphenanthrene (3 g.) with anhydrous hydrogen fluoride (50 ml.), followed by reduction with zinc dust in 5N-sodium hydroxide, as described above, gave 1 : 2-3 : 4-dibenzanthracene (1·2 g., 45%), m. p. 202—203°, pale yellow needles (from acetic acid); $\lambda_{max.}$ 265° (ε 66,200), 2750 (ε 98,600), 2860 (ε 130,300), and 3200 Å (ε 7170).

Attempted preparation of 9-(1-*bromo*-2-*naphthylmethyl*)*phenanthrene*. 1-Bromo-2-naphthaldehyde (12 g.) in benzene (150 ml.) was added dropwise to 9-phenanthrylmagnesium bromide (prepared from 9-bromophenanthrene, 14 g., etc.) in ether (20 ml.) and benzene (20 ml.). The mixture was heated under reflux for 4 hr. Working up the product as for the homologue (above), and reducing the secondary alcohol with red phosphorus and iodine, gave a product which was chromatographed on alumina in 1 : 1 benzene–light petroleum (b. p. 40—60°), giving a substance (6 g.) as plates, m. p. 155—157° (this m. p. could not be raised) (Found: C, 82·7; H, 5·1; Br, 12·1%).

9-(2-*Carboxy*-1-*naphthylmethyl*)*phenanthrene* (?). Carbon dioxide (from barium carbonate 0·394 g., generated with concentrated sulphuric acid) was condensed into the Grignard reagent prepared from the above bromo-compound (1 g.), magnesium (0·1 g.), iodine (1 crystal), and methyl iodide (1—2 drops) in benzene (15 ml.) and ether (10 ml.). Working up and isolation of the acid as above gave an *acid* (0·5 g.), m. p. 236—238°, which crystallised from benzene or benzene–*cyclo*hexane in plates (0·13 g.), m. p. 243—244° after several recrystallisations (Found: C, 85·6; H, 5·25. $C_{26}H_{18}O_2$ requires C, 86·2; H, 5·0%). From the neutral fraction was obtained a substance (0·4 g.), m. p. 175° (from ethanol) (Found: C, 93·5; H, 5·7. Calc. for $C_{25}H_{18}$: C, 94·3; H, 5·7%), which may be impure 9-(2-naphthylmethyl)phenanthrene.

In hydrogen fluoride this acid was largely destroyed.

The author thanks Dr. W. P. Grove and Dr. J. R. Catch for their interest, and the Atomic Energy Authority for the award of a Harwell fellowship.

THE RADIOCHEMICAL CENTRE,
AMERSHAM, BUCKS.

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757. p-*Hydrazophenetole.*

By M. Khalifa and A. A. Abo-Ouf.

Reduction of *o*-azophenetole with alcoholic ammonium sulphide to the hydrazo-derivative and failure of the *para*-isomer to undergo a similar change have been reported,[1] though later success in reducing *p*-azophenetole was claimed [2] but without experimental details. In numerous attempts we failed to reduce the *para*-compound by this reagent.

Khalifa and Linnell [3] found that lowering the electron-density on the azo-group favours its reduction to the hydrazo-stage by zinc. In conformity we find that *p*-azoxyphenetole is reduced by zinc in ethanolic potassium hydroxide approx. twice as fast as *p*-azophenetole. The resulting *p*-hydrazophenetole has the m. p. reported earlier.[2]

Experimental.—p-*Hydrazophenetole.* To *p*-azophenetole (0·1 g.), dissolved in stirred, boiling alcohol (10 ml.), zinc dust (1 g.) was added, followed by 30% alcoholic potassium hydroxide (12 drops per min.) until the mixture was no longer coloured. The filtrate was rapidly cooled in ice. The hydrazo-compound separated in needles, m. p. 118—119°.

The above reduction was complete in about 30 min. With the azoxy-compound it required only 15 min.

We thank Professor Y. M. Abou-Zeid of this Faculty for facilities.

Organic Chemistry Department, Faculty of Pharmacy,
Cairo University. [*Received, April 9th,* 1958.]

[1] Schmitt and Möhlau, *J. prakt. Chem.*, 1878, **18**, 202.
[2] Kinzel, *Arch. Pharm.*, 1891, **229**, 351.
[3] Khalifa, Thesis, London, 1955.

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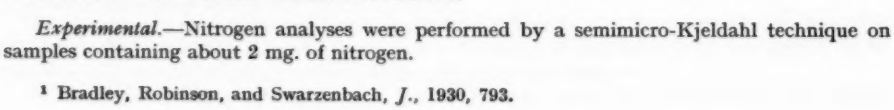
758. β-(3 : 4-*Dihydroxy*-5-*methoxyphenyl*)*alanine.*

By P. Smith.

β-(3 : 4-Dihydroxy-5-methoxyphenyl)alanine (IV), a compound of possible physiological interest in view of its relation to β-(3 : 4-dihydroxyphenyl)alanine, adrenaline, and mescaline, has been synthesised from 3 : 4-dihydroxy-5-methoxybenzaldehyde (I). Condensation of the latter with acetylglycine and mild hydrolysis of the crude azlactone gave the acetamidocinnamic acid (II), catalytic hydrogenation of which afforded the triacetyl derivative (III) from which the hydrochloride of the required amino-acid was obtained by hydrolysis with dilute hydrochloric acid.



Previous preparations of the aldehyde (I) by alkaline hydrolysis of 5-bromovanillin [1] require the use of an autoclave which was not available. However 5-iodovanillin undergoes the required hydrolysis at atmospheric pressure and was itself readily prepared by iodination of vanillin under mild alkaline conditions.

Experimental.—Nitrogen analyses were performed by a semimicro-Kjeldahl technique on samples containing about 2 mg. of nitrogen.

[1] Bradley, Robinson, and Swarzenbach, *J.*, 1930, 793.

5-*Iodovanillin.* Iodine (12·6 g.) was added in four portions during 30 min. to a rapidly stirred suspension of vanillin (7·5 g.) in water (200 ml.) containing sodium hydrogen carbonate (5 g.) and potassium iodide (10 g.). Stirring was continued for 3 hr. and the mixture left overnight. The filtered product was washed with dilute sodium thiosulphate and water and dried at 45° (11·8 g., m. p. 175°). Crystallised from aqueous ethanol, it had m. p. 180° (Bougault and Robin [2] give m. p. 180°).

3 : 4-*Dihydroxy-5-methoxybenzaldehyde* (I). A mixture of 5-iodovanillin (26·7 g.), copper powder (10 g.), and aqueous sodium hydroxide (20% w/v; 270 ml.) was refluxed for 4 hr. After cooling, acidification with concentrated hydrochloric acid, addition of a little sodium sulphite, and filtration, the solution was extracted continuously with ether. Usually the gradual separation of solid promoted extensive emulsification and complete extraction of the product became impracticable, but on one occasion 15 g. of light-grey material, m. p. 120—127°, were obtained. Crystallisation from ethyl acetate–chloroform (charcoal) gave the aldehyde (11·0 g.) as almost colourless platelets, m. p. 128—131°, raised to 132° by recrystallisation from ethyl acetate (Bradley, Robinson, and Swarzenbach [1] give m. p. 132—134°).

α-*Acetamido*-3 : 4-*diacetoxy-5-methoxycinnamic acid* (II). A mixture of the above aldehyde (5 g.), acetylglycine (3·75 g.), fused sodium acetate (2·4 g.), and acetic anhydride (22·5 ml.) was heated at 100° for 90 min. The yellow crystalline azlactone obtained after cooling and gradual addition of water (45 ml.) was filtered off and washed with acetic acid (33% v/v) and then with water; this was dissolved in hot dioxan (20 ml.) and kept at 100° for 15 min. while water (20 ml.) was gradually added. The hot solution was treated with charcoal (2 g.) and hot water added until the supernatant liquid was pure yellow. After filtration the solution gradually deposited yellow crystals (3·6 g.), m. p. 181—184° after being dried (P_2O_5). Crystallisation from ethanol–benzene–light petroleum (b. p. 60—80°) with charcoal treatment gave the *acetamidocinnamic acid* as colourless prisms, m. p. 184—185° (Found: N, 3·8. $C_{16}H_{17}O_6N$ requires N, 4·0%).

N-*Acetyl*-β-(3 : 4-*diacetoxy-5-methoxyphenyl*)*alanine* (III). Absorption occurred slowly when the acetamidocinnamic acid (3·52 g.) was shaken in ethanol–ethyl acetate with hydrogen in the presence of 5% palladium–charcoal (1·0 g.). After 24 hr., filtration and evaporation afforded a gum which solidified when triturated with ethyl acetate. The *product* (3·1 g., m. p. 180—182°) after recrystallisation from ethanol–benzene had m. p. 190—192° (Found: N, 3·85. $C_{16}H_{19}O_8N$ requires N, 3·95%).

β-(3 : 4-*Dihydroxy-5-methoxyphenyl*)*alanine* (IV). The triacetyl derivative (1·3 g.) was refluxed under nitrogen with N-hydrochloric acid (15 ml.) for 3 hr., and the residue after evaporation (0·95 g., m. p. 225—230° decomp.) dried *in vacuo* (P_2O_5; KOH). Crystallisation from methanol–ether afforded the *amino-acid hydrochloride*, m. p. 228—229° (decomp.) (Found: N, 5·25. $C_{10}H_{14}O_5NCl$ requires N, 5·3%), some of which was converted into the free *amino-acid monohydrate* by passing an aqueous solution through a short column of the weakly basic resin Deacidite " E " (acetate form); the residue after evaporation of the filtrate and washings was crystallised from water (m. p. 222—224°) (Found: N, 5·75. $C_{10}H_{13}O_5N,H_2O$ requires N, 5·7%). Its weight (123 mg.) was unchanged after desiccation (P_2O_5) for 18 hr. at 10 mm., but it subsequently lost 8 mg. (calc., 9 mg.) when heated at 100°/0·1 mm. for 2 hr. These properties resemble those of 2 : 5-dihydroxyphenylalanine monohydrate.[3]

The author thanks Mrs. G. A. Hill and Mr. J. Ratcliffe for experimental assistance and the Director-General of Medical Services, Royal Air Force, for permission to publish this work.

ROYAL AIR FORCE INSTITUTE OF AVIATION MEDICINE,
FARNBOROUGH, HANTS.

[*Received, May 9th*, 1958.]

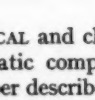
[2] Bougault and Robin, *Compt. rend.*, 1921, **172**, 452.
[3] Neuberger, *Biochem. J.*, 1948, **43**, 599.

759. *Pyrimidines. Part III.* The Synthesis and Some Reactions of 5-Ethynylpyrimidines.*

By R. Hull.

Biological and chemical [1] interests in acetylenic compounds have been mainly confined to aliphatic compounds. Few ethynyl heterocyclic compounds have been synthesised. This paper describes the preparation of two 5-ethynylpyrimidines.

5-Acetyl-4-methyl-2-phenylpyrimidine [2] (I) was converted into the 5-1′-chlorovinylpyrimidine (II) by phosphorus pentachloride, which with alcoholic potassium hydroxide gave 5-ethynyl-4-methyl-2-phenylpyrimidine (III).



(I): R = Ph, R′ = COMe
(II): R = Ph, R′ = CCl:CH$_2$
(III): R = Ph, R′ = C:CH

(IV): R = Ph, R′ = CH:CH·S·COMe
(V): R = NMe$_2$, R′ = COMe
(VI): R = NMe$_2$, R′ = C:CH

The infrared spectrum (0·05 mm. molten layer) of compound (III) contains bands at 2·9 and 4·65 μ which can be attributed to the 5-acetylenic group. Compound (III) formed a silver salt and was converted into the monoadduct (IV) by thioacetic acid.[3] These observations confirm structure (III).

The 2-dimethylamino-analogue (VI) was prepared by a similar series of reactions from the 5-acetylpyrimidine (V).

Experimental.—*5-1′-Chlorovinyl-4-methyl-2-phenylpyrimidine.* Phosphorus pentachloride (37 g.) was added slowly to a stirred warm solution of 5-acetyl-4-methyl-2-phenylpyrimidine [2] (37 g.) in dry benzene (200 ml.), and the whole was heated under reflux during 2 hr. The cooled mixture was poured into ice and water (250 ml.), and the aqueous phase neutralised with sodium carbonate. After 30 minutes' stirring the benzene layer was separated and the aqueous phase re-extracted with benzene. The extracts were combined and dried and excess of solvent was removed by distillation. The main fraction of the residue (36 g.) distilled from a bath at 145°/0·1 mm. to give the *chlorovinylpyrimidine* as a pale brown oil (Found: C, 67·8; H, 5·1; N, 12·7; Cl, 14·9. $C_{13}H_{11}N_2Cl$ requires C, 67·7; H, 4·8; N, 12·2; Cl, 15·4%).

5-Ethynyl-4-methyl-2-phenylpyrimidine. A solution of 5-1′-chlorovinyl-4-methyl-2-phenylpyrimidine (3·3 g.) in alcohol (15 ml.) was added to potassium hydroxide (2·4 g.) in 95% alcohol (15 ml.), and the whole was heated under reflux during 2 hr. and then evaporated to dryness. Water was added to the residue and the product was extracted with ether. The extract was dried and evaporated and the residue (2 g.) distilled at 150—155° (bath-temp.)/0·18 mm., giving the *ethynylpyrimidine* which set to needles. Recrystallisation from light petroleum (b. p. 40—60°) gave the product as needles, m. p. 64—65°, $\lambda_{max.}$ (in MeOH) 280 mμ (ε 26,500), shoulder at 287 mμ, $\lambda_{min.}$ 235 mμ (ε 3100) (Found: C, 80·0; H, 5·3; N, 14·6. $C_{13}H_{10}N_2$ requires C, 80·4; H, 5·15; N, 14·45%); the infrared spectrum, determined on a 0·05 mm. molten layer, showed bands centred about 2·9 and 4·65 μ. Ammoniacal silver nitrate in 50% aqueous alcohol (prepared from 0·36 g. of silver nitrate) was added slowly to a stirred solution of 5-ethynyl-4-methyl-2-phenylpyrimidine (0·4 g.) in warm ethanol (7 ml.). The *silver salt* was collected and washed with water and alcohol (Found: Ag, 34·4. $C_{13}H_9N_2Ag,0·5H_2O$ requires Ag, 34·8%).

2-(4-Methyl-2-phenyl-5-pyrimidylvinyl) thiolacetate. Thioacetic acid (0·8 g.) and 5-ethynyl-4-methyl-2-phenylpyrimidine (2·04 g.) were mixed and heated gently to a single phase. After 7 days the mixture had set to a mass of yellow needles. The *product* distilled as a pale yellow oil from a bath at 130/0·1 mm., setting to yellow needles (Found: C, 66·3; H, 5·1; N, 10·6. $C_{15}H_{14}ON_2S$ requires C, 66·65; H, 5·2; N, 10·4%).

5-Acetyl-2-dimethylamino-4-methylpyrimidine. Dimethylguanidine sulphate [4] (6·8 g.) and ethoxymethyleneacetylacetone (7·85 g.) were added to a cooled solution of sodium (1·15 g.) in

* Part II, *J.*, 1957, 4845.

[1] Bu'Lock, *Quart. Rev.*, 1956, **10**, 371; Johnson, *Sci. Progr.*, 1954, **42**, 469.
[2] Mitter and Bardhan, *J.*, 1923, 2179.
[3] Bader, Cross, Heilbron, and Jones, *J.*, 1949, 619.
[4] Phillips and Clarke, *J. Amer. Chem. Soc.*, 1923, **45**, 1756.

alcohol (20 ml.), and the whole was heated under reflux during 2 hr. After cooling, the mixture was filtered, the filtrate was evaporated to dryness, and the solids were combined; inorganic material was removed by washing with water. The *acetylpyrimidine* (7 g.) recrystallised from water in needles, m. p. 56—57° (Found: C, 60·1; H, 7·7; N, 23·0. $C_9H_{13}ON_3$ requires C, 60·35; H, 7·3; N, 23·45%). The *semicarbazone* crystallised from alcohol in needles, m. p. 226—227° (Found: C, 51·1; H, 7·7. $C_{10}H_{16}ON_6$ requires C, 50·9; H, 6·8%).

5-1'-Chlorovinyl-2-dimethylamino-4-methylpyrimidine. 5-Acetyl-2-dimethylamino-4-methylpyrimidine (2·58 g.) and phosphorus pentachloride (3 g.) were heated under reflux in benzene (30 ml.) during 2 hr. The cooled mixture was poured, with stirring, into ice-water and neutralised with sodium carbonate. The benzene layer was separated and combined with further benzene extracts of the aqueous phase and dried. After removal of solvent the residue (1·9 g.) distilled from a bath at 100°/0·08 mm., to give the *chlorovinylpyrimidine* as a colourless oil (Found: C, 55·4; H, 6·3; N, 21·0; Cl, 18·1. $C_9H_{12}N_3Cl$ requires C, 54·7; H, 6·1; N, 21·25; Cl, 18·1%).

2-Dimethylamino-5-ethynyl-4-methylpyrimidine. 5-1'-Chlorovinyl-2-dimethylamino-4-methylpyrimidine (14·7 g.) in alcohol (50 ml.) was heated with potassium hydroxide (12·5 g.) in 95% alcohol (80 ml.) under reflux during 2 hr., then evaporated to dryness. Water was added and the product extracted with ether. After removal of solvent the *ethynylpyrimidine* (9·4 g.) distilled at 80—84°/0·1 mm. as a dark red oil (Found: C, 65·3; H, 6·6; N, 24·7. $C_9H_{11}N_3,0{\cdot}25H_2O$ requires C, 65·25; H, 6·8; N, 25·35%). The compound did not give a Beilstein test for halogen and formed a silver salt with ammoniacal silver nitrate.

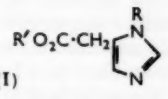
The author thanks Mr. M. St. C. Flett for the infrared, and Dr. J. M. Pryce for the ultraviolet, absorption determinations.

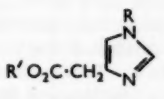
IMPERIAL CHEMICAL INDUSTRIES LIMITED, PHARMACEUTICALS DIVISION,
ALDERLEY PARK, MACCLESFIELD, CHESHIRE. [*Received, May 15th*, 1958.]

760. *Synthesis of* 1-β-D-*Ribofuranosyl*-4(5)-*glyoxalinylacetic Acid, a Metabolite of Histamine.*

By J. BADDILEY, J. G. BUCHANAN, D. H. HAYES, and P. A. SMITH.

AMONG the metabolites which appear in the urine of rats and mice after interperitoneal injection of histamine [1] is a ribofuranosyl derivative of 4-glyoxalinylacetic acid [2-4] (I or II; R = ribofuranosyl, R′ = H). The compound was characterised as the crystalline hydrochloride and shown to give the acid (I; R = R′ = H) and ribose on acidic [2,4] or enzymic [3] hydrolysis. The glycoside consumed one mol. of periodate. Two structural features were not decided by the degradative evidence: (i) the relative positions of the ribosyl group and the acetic acid side chain and (ii) the anomeric configuration of the ribosyl group. This paper describes a synthesis which establishes the configuration of the ribosyl linkage.


(I)


(II)

The mercurichloride salt [5] of methyl 4-glyoxalinylacetate was condensed with tri-*O*-benzoyl-β-D-ribofuranosyl chloride [6] in boiling xylene. The product was debenzoylated

[1] Schayer, *J. Biol. Chem.*, 1952, **196**, 469; Mehler, Tabor, and Bauer, *ibid.*, 1952, **197**, 475; Tabor, Mehler, and Schayer, *ibid.*, 1953, **200**, 605; Bouthillier and Goldner, *Arch. Biochem. Biophys.*, 1953, **44**, 251; Karjala and Turnquest, *J. Amer. Chem. Soc.*, 1955, **77**, 6358; Schayer and Karjala, *J. Biol. Chem.*, 1956, **221**, 307.
[2] Karjala, *J. Amer. Chem. Soc.*, 1955, **77**, 504.
[3] Tabor and Hayaishi, *ibid.*, p. 505.
[4] Karjala, Turnquest, and Schayer, *J. Biol. Chem.*, 1956, **219**, 9.
[5] Cf. Davoll and Lowy, *J. Amer. Chem. Soc.*, 1951, **73**, 1650, and subsequent papers.
[6] Kissman, Pidacks, and Baker, *ibid.*, 1955, **77**, 18.

and the methyl ester group hydrolysed with acid. Isolation of the ribosyl compound was effected by ion-exchange chromatography, finally as the hydrochloride. Comparison with the natural compound, kindly given to us by Dr. H. Tabor, showed the two to be indistinguishable in melting point, infrared spectrum, and R_F values in a number of solvent systems, as well as in their behaviour on acid hydrolysis.

Reaction of a tri-*O*-acetyl- or tri-*O*-benzoyl-ribofuranosyl halide with mercury salts [5] yields only the β-anomer in all cases so far studied. This establishes the β-configuration of the natural compound.

Experimental.—Methyl 4*-glyoxalinylacetate.* Crude 4-glyoxalinylacetic acid hydrochloride (42·8 g.), prepared by acid hydrolysis of the cyanide,[7] was heated under reflux with methanol (200 c.c.) for 1 hr. Paper chromatography showed almost complete esterification. The solution was evaporated to dryness, the residue dissolved in water, and the solution basified with sodium hydrogen carbonate, then evaporated. The dry residue was extracted with warm ethyl acetate (8 × 50 c.c.) and the filtered extracts were evaporated to an oil (28·5 g., 75%). The oil was dissolved in methanol (50 c.c.), and a solution of oxalic acid dihydrate (27·0 g.) in methanol (75 c.c.) added. The *oxalate*, m. p. 164—168°, crystallised as plates (24·5 g.). Recrystallised from water–acetone or methanol it had m. p. 173—174° (Found: N, 12·4. $C_8H_{10}O_6N_2$ requires N, 12·1%). It gave a *picrate*, m. p. 167·5—168·5°, lemon-yellow prisms from ethanol (Found: C, 38·7; H, 3·0; N, 18·8. $C_{12}H_{11}O_9N_5$ requires C, 39·0; H, 3·0; N, 19·0%).

Mercurichloride salt of methyl 4*-glyoxalinylacetate.* The above oxalate (2·3 g.) was dissolved in water (25 c.c.), and the solution basified with sodium carbonate, saturated with ammonium chloride, and extracted with ethyl acetate (8 × 20 c.c.). The extract was dried (Na_2SO_4) and evaporated to an oil (1·12 g., 80%). Paper chromatography showed only one spot. The free ester was dissolved in 50% aqueous methanol (40 c.c.), and a solution of sodium hydroxide (0·392 g.) in methanol (20 c.c.) added at 10°, followed by mercuric chloride (2·68 g.) in methanol (60 c.c.). The precipitate was centrifuged immediately and washed with portions (100 c.c.) of methanol, water, methanol, and ether. The white amorphous solid (3·5 g., 93%) was virtually free from 4-glyoxalinylacetic acid as shown by chromatography.

1-β-D-*Ribofuranosyl*-4(5)-*glyoxalinylacetic acid.* The above mercury salt (3·5 g.) was powdered and suspended in dry sulphur-free xylene (200 c.c.). " Hyflo Supercel " (7 g.) was added and xylene (50 c.c.) was distilled off at atmospheric pressure. A solution of tri-*O*-benzoylribofuranosyl chloride [from the 1-*O*-acetyl compound (4·71 g.)] in xylene (56 c.c.) was added and the mixture was boiled, with stirring, for 1 hr. The suspension was filtered while hot and the residue washed with xylene (20 c.c.). The filtrate was evaporated to a gum (4·17 g.). By crystallisation from methanol 1-*O*-acetyl-2 : 3 : 5-tri-*O*-benzoyl-β-D-ribose (0·28 g.) was obtained. The remaining material was debenzoylated with sodium methoxide (from 0·075 g. of sodium) in methanol (total volume 160 c.c.). When debenzoylation was complete (paper chromatography) the solution was filtered and evaporated to dryness and the residue dissolved in 4N-hydrochloric acid (40 c.c.). Extraction with chloroform removed methyl benzoate and benzoic acid. The aqueous solution was evaporated to dryness and to the residue (1·6 g.) was added concentrated hydrochloric acid (25 c.c.). The mixture was boiled under reflux for 10 min., cooled, and filtered (charcoal), and the filtrate evaporated to dryness several times with water to give a gummy residue (1·0 g.). This material (0·5 g.) was dissolved in water (75 c.c.) and the pH adjusted to 4. It was chromatographed on a Dowex-50(X8) (H^+) column (200—400 mesh; 33 × 2 cm.). Separation from glyoxalinylacetic acid was carried out by gradient elution, using water and 2·9N-hydrochloric acid. 25 c.c. Fractions were collected and the riboside was detected by using the periodate–Schiff spray.[8] The appropriate fractions were evaporated to dryness, the residue dissolved in water, and the pH made slightly alkaline with sodium hydroxide. The riboside was adsorbed on a column of Dowex-1(X2) acetate (22 × 2·5 cm.), and the column washed with water. The riboside was eluted with 2N-acetic acid, being detected as before.[8] The appropriate fractions were evaporated to dryness and the *ribosylglyoxaline hydrochloride* (96 mg.) obtained by crystallisation from dilute hydrochloric acid–acetone. It had m. p. 177—179°, undepressed on admixture with the natural compound,

[7] Pyman, *J.*, 1911, **99**, 668.
[8] Baddiley, Buchanan, Handschumacher, and Prescott, *J.*, 1956, 2818.

and $[\alpha]_D^{22}$ −52·6° (*c* 0·5 in MeOH) (Found: C, 40·6; H, 5·3; N, 9·8. $C_{10}H_{15}O_6N_2Cl$ requires C, 40·7; H, 5·1; N, 9·5%). The ribosyl compound consumed 0·98 mol. of sodium metaperiodate.[9] The infrared spectrum (KBr disc) was identical with that of the natural compound. When it was hydrolysed with 0·1N-hydrochloric acid at 145° for 5 hr.[2,4] glyoxalinylacetic acid and ribose were formed.

Paper chromatography. Whatman No. 4 paper was used. Glyoxalines lacking a nitrogen-substituent were detected by the Pauly spray,[10] ribose by aniline phthalate,[11] and ribosides by the periodate–Schiff spray.[8] Solvents: (A) *n*-propyl alcohol (75)–ammonia (*d* 0·88) (25); (B) *n*-propyl alcohol (6)–ammonia (*d* 0·88) (3)–water (1); (C) *n*-butyl alcohol (4)–acetic acid (1)–water (5) (upper layer).

	R_F in solvents		
	A	B	C
4-Glyoxalinylacetic acid	—	0·64	0·32
Methyl 4-glyoxalinylacetate	—	0·91	0·59
1-Ribosyl-4(5)-glyoxalinylacetic acid	0·21	0·52	0·26
Ribose	—	0·54	0·30

We thank the Nuffield Foundation and the British Empire Cancer Campaign for financial assistance.

KING'S COLLEGE, UNIVERSITY OF DURHAM,
NEWCASTLE UPON TYNE.

[*Received, May 15th,* 1958.]

[9] Dixon and Lipkin, *Analyt. Chem.*, 1954, **26**, 1092.
[10] Dent, *Biochem. J.*, 1947, **41**, 240.
[11] Partridge, *Nature*, 1949, **164**, 443.

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761. *The Reduction of* N*-Phenylhydroxylamine with Lithium Aluminium Hydride.*

By M. L. BURSTALL and M. S. GIBSON.

REDUCTION of nitrobenzene,[1] nitrosobenzene,[2] and azoxybenzene[1] with lithium aluminium hydride has in each case been reported to give azobenzene. The binuclear products of reduction of nitrobenzene in aqueous media seem generally to be attributed to the formation and subsequent reactions of *N*-phenylhydroxylamine.[3] It was of interest, therefore, to determine the course of reduction of this compound with lithium aluminium hydride. The products are azobenzene and aniline in nearly equimolar amounts. The non-formation of aniline in the reductions reported previously[1,2] has been confirmed.

The absence of aniline from the reduction products of nitrobenzene and nitrosobenzene may be taken to suggest that *N*-phenylhydroxylamine is not formed as a reaction intermediate in either case. If *N*-phenylhydroxylamine is formed transiently and undergoes preferential reduction, a mechanism must be postulated for the complete removal of the aniline so formed, *e.g.*, condensation with nitrosobenzene; but if it condenses with nitrosobenzene (giving azoxybenzene), the absence of aniline in the reduction products is accommodated.

It may be noted that the reduction of *N*-phenylhydroxylamine (to aniline and azobenzene) can be explained on the basis of its disproportionation to aniline and azoxybenzene before reduction.[3]

Experimental.—Nitrobenzene was distilled before use; nitrosobenzene, azoxybenzene, and *N*-phenylhydroxylamine were freshly prepared and crystallised.

N-Phenylhydroxylamine (3·1 g.) in ether (25 ml.) was added to lithium aluminium hydride (4·0 g.) in boiling ether (100 ml.) during 10—15 min. After a further ½ hr., excess of reagent was destroyed with ethyl acetate. A little water was added, and the granular precipitate

[1] Nystrom and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3738.
[2] Weil, Prijs, and Erlenmeyer, *Helv. Chim. Acta*, 1953, **36**, 142.
[3] Sidgwick, "Organic Chemistry of Nitrogen," Oxford, 1949, pp. 252 *et seq.*

XUM

was filtered off and washed with ether. The combined filtrate and washings were dried ($MgSO_4$) and evaporated, and the red residue (2·4 g.) was chromatographed on alumina, yielding (i) azobenzene [1·33 g., eluted with light petroleum (b. p. 60—80°)–benzene], (ii) and (iii) gummy fractions (0·1 g., 0·1 g., eluted with benzene and ether respectively), and (iv) aniline (0·7 g., eluted with chloroform). Azobenzene formed orange-red leaflets (from ethanol), m. p. and mixed m. p. 68° (Found: C, 78·2; H, 5·4. Calc. for $C_{12}H_{10}N_2$: C, 78·0; H, 5·5%). Fraction (iv) was identified as aniline from its infrared spectrum, and by conversion into acetanilide, plates (from water), m. p. and mixed m. p. 113—114°.

In like manner, nitrobenzene, nitrosobenzene, and azoxybenzene gave azobenzene in yields of 85% (lit., 84%), 72% (lit., 69%) and 96% (lit., 99%) respectively; in the first two cases, chromatographic fractions following azobenzene afforded some gum. No aniline was detected in these reductions.

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BASIC RESEARCH DEPARTMENT, THOMAS HEDLEY & CO., LTD.,
NEWCASTLE UPON TYNE, 1. [*Received, May 20th*, 1958.]

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762. *Formation and Properties of a Dipyridine–Germanium Tetrachloride Adduct.*

By E. W. ABEL.

DESPITE considerable interest [1] in the reactions of germanium tetrachloride for the preparation of substitution products of germane, there has been little investigation of co-ordination of the tetrahalides. Thomas and Southwood [2] stated that tertiary amines were without action on germanium tetrachloride; Trost,[3] however, reported formation of $GeCl_4(NEt_3)_4$, and Johnson and Sidwell recorded [4] the compound $GeI_4(NEt_3)_5$.

We have found that an excess of pyridine with germanium tetrachloride produces a dipyridine–germanium tetrachloride adduct in excellent yield, in accord with the stability of the similar dipyridine compounds of silicon [5] and stannic tetrachlorides.[6] The absence of reaction between diethylaniline and germanium tetrachloride [2] was presumably due to the considerable greater steric hindrance in diethylaniline than in pyridine. The dipyridine–germanium tetrachloride adduct is white, crystalline, and insoluble in ether and pentane, but soluble in benzene and chloroform. It is rapidly hydrolysed in air.

With boiling alcohols in the presence of further pyridine it slowly gives pyridine hydrochloride and the germanium alkoxides (Table 1). Previous [7,8] methods for the formation of these alkoxides have involved very fast reactions; thus the slow reaction of the pyridine complex presents a possible method for the kinetic study of the alkoxide formation.

Ethanethiol and butane-1-thiol similarly produce the germanium sulphides in good yields (better than those of previous methods [9,10]). Tetrakisdiethylaminogermane was formed by the interaction of the complex with further pyridine and diethylamine.

Experimental.—Interaction of germanium tetrachloride and pyridine. The tetrachloride (13·06 g., 1 mol.) in pentane (50 c.c.) was added to pyridine (12·00 g., 2·5 mol.) in pentane (50 c.c.) at 0°. After 24 hr. the white precipitate was filtered off and washed with pentane (3 × 50 c.c.). Excess of solvent was removed at 0·2 mm., to leave the *dipyridine–germanium tetrachloride adduct* (22·36 g., 98%), m. p. 207—214° (decomp., sealed tube) [Found: C, 32·7;

[1] Johnson, *Chem. Rev.*, 1951, **48**, 259.
[2] Thomas and Southwood, *J.*, 1931, 2083.
[3] Trost, *Canad. J. Chem.*, 1952, **30**, 835.
[4] Johnson and Sidwell, *J. Amer. Chem. Soc.*, 1933, **55**, 1884.
[5] Harden, *J.*, 1887, **51**, 40.
[6] Pfeiffer, *Z. anorg. Chem.*, 1911, **71**, 97.
[7] Johnston and Fritz, *J. Amer. Chem. Soc.*, 1953, **75**, 718.
[8] Bradley, Kay, and Wardlaw, *Chem. and Ind.*, 1953, **746**.
[9] Backer and Stienstra, *Rec. Trav. chim.*, 1933, **52**, 1033.
[10] *Idem, ibid.*, 1935, **54**, 607.

H, 3·1; N, 7·4; Cl, 38·8%; *M*, 379 (ebullioscopic in benzene). $C_{16}H_{16}Cl_4GeN_2$ requires C, 32·2; H, 2·7; N, 7·5; Cl, 38·1%; *M*, 373].

Formation of germanium alkoxides. The complex (1 mol.), pyridine (2 mol.), and the alcohol (4 mol.) in benzene (75 c.c.) were refluxed for 100 hr. (reaction times less than 75 hr. gave much reduced yields). Volatile matter was removed at 20°/0·2 mm., and the residue was shaken with ether (50 c.c.) in order to precipitate pyridine hydrochloride. This was filtered off; removal of solvent at 20°/0·5 mm. left the crude alkoxide, which was distilled to give the pure product (Table 1). Each of these reactions was carried out on approx. 0·05 molar scale.

TABLE 1. *Germanium tetra-alkoxides.*

Alkyl	Yield (%)	B. p./mm.	n_D^{20}	Found (%) C	Found (%) H	Calc. (%) C	Calc. (%) H
Ethyl	73	75°/10	1·4061	37·6	7·7	38·0	7·9
n-Propyl	79	111°/10	1·4168	46·9	8·7	46·6	9·1
n-Butyl	91	88°/0·2	1·4271	52·1	9·7	52·6	9·9

Formation of the alkylthiogermanes. The complex (1 mol.), pyridine (2 mol.), and the thiol (4 mol.) in light petroleum (50 c.c.) (b. p. 60—80°) were heated at 150° for 25 hr. After cooling, pyridine hydrochloride and then solvent (at 20°/5 mm.) were removed. Distillation produced the pure products (Table 2). These reactions were carried out on approx. 0·05 molar scale.

TABLE 2. *Tetra-alkylthiogermanes.*

Alkyl	Yield (%)	B. p./mm.	n_D^{20}	Found (%) C	Found (%) H	Calc. (%) C	Calc. (%) H
Ethyl	73	151°/0·1	1·5886	30·9	6·0	30·3	6·3
n-Butyl	76	198°/0·5	1·5450	44·5	8·1	44·8	8·4

Formation of tetrakisdiethylaminogermane. The complex (3·94 g., 1 mol.), pyridine (1·67 g., 2 mol.), and diethylamine (3·08 g., 4 mol.) in pentane (50 c.c.) were heated at 120° for 30 hr. After cooling and filtration, removal of the solvent at 20°/0·5 mm. and distillation produced tetrakisdiethylaminogermane (2·63 g., 69%), b. p. 72°/0·7 mm., n_D^{20} 1·4726 (Found: C, 53·8; H, 10·8; N, 15·3. Calc. for $C_{16}H_{40}GeN_4$: C, 53·3; H, 11·1; N, 15·5%).

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INORGANIC CHEMISTRY RESEARCH LABORATORIES,
IMPERIAL COLLEGE, LONDON, S.W.7.

[*Received, May 23rd*, 1958.]

763. *Per-rhenyl Fluoride.*

By E. E. AYNSLEY and M. L. HAIR.

PER-RHENYL FLUORIDE, ReO_3F, first obtained pure by Engelbrecht and Grosse,[1] is obtained in good yield together with iodine oxytrifluoride, IOF_3, and iodyl fluoride, IO_2F, by the reaction of potassium per-rhenate with iodine pentafluoride:

$$KReO_4 + IF_5 = ReO_3F + IOF_3 + KF$$
$$2IOF_3 = IO_2F + IF_5$$

Moreover, we have redetermined the m. p. and b. p. of rhenium oxypentafluoride, $ReOF_5$, and rhenium dioxytrifluoride, ReO_2F_3 (prepared from rhenium dioxide and elementary fluorine [2]), and a comparison of the three oxyfluorides of septavalent rhenium is given in the Table.

Oxyfluorides of septavalent rhenium.

	M. p.	B. p.	Colour
$ReOF_5$	35°	55°	Cream
ReO_2F_3	95	126	Pale yellow
ReO_3F	147	164	Yellow [1]

[1] Engelbrecht and Grosse, *J. Amer. Chem. Soc.*, 1954, **76**, 2042.
[2] Aynsley, Peacock, and Robinson, *J.*, 1950, 1622.

XUM

Experimental.—Preparation of per-rhenyl fluoride. Iodine pentafluoride (9 g.), prepared by burning dry iodine in a fluorine–nitrogen stream (40 : 60, v/v) and freed from dissolved fluorine and iodine heptafluoride by vacuum fractionation, was condensed on powdered potassium per-rhenate (2 g.). Only slight reaction occurred at room temperature, the solution becoming pale yellow. However, on heating the mixture under such conditions that the iodine pentafluoride was allowed to reflux in the reaction bulb (97°), the potassium per-rhenate dissolved completely to form a deep yellow solution from which a yellow sludge separated on cooling. Removal of excess of iodine pentafluoride under vacuum left a yellow residue which, when heated to 140° in a paraffin bath, yielded, first, further iodine pentafluoride, and then a yellow solid which formed as a glass in a trap cooled to 0° (Found: Re, 73·2; F, 7·9. Calc. for ReO_3F: Re, 73·6; F, 7·5%). The product had m. p. 147°, b. p. 164°, in agreement with the values given by Engelbrecht and Grosse.[1]

In the preparation of permanganyl fluoride, MnO_3F, from the reaction between potassium permanganate and iodine pentafluoride, an explosion always occurs if the potassium permanganate is in excess; [3] in the preparation of per-rhenyl fluoride from potassium per-rhenate and iodine pentafluoride there is never any danger of an explosion.

Preparation of iodine oxytrifluoride and iodyl fluoride. The white solid remaining in the reaction vessel was a mixture of potassium fluoride and iodyl fluoride. The latter was dissolved in boiling iodine pentafluoride, then separated from undissolved potassium fluoride and recrystallised as iodine oxytrifluoride, IOF_3 (Found: I, 63·4; F, 28·8. Calc. for IOF_3: I, 63·6; F, 28·5%). Heating the iodine oxytrifluoride to 110° in a vacuum again caused evolution of iodine pentafluoride, and iodyl fluoride remained as a fine powder (Found: I, 71·6; F, 10·9. Calc. for IO_2F: I, 71·3; F, 10·7%).

One of us (M. L. H.) thanks the Salters' Company for a Scholarship.

KING'S COLLEGE, NEWCASTLE UPON TYNE, 1. [*Received, May 27th,* 1958.]

[3] Aynsley, *J.*, 1958, 2425.

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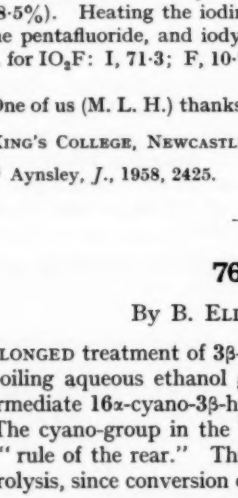
764. 16α-*Carboxyprogesterone.*

By B. ELLIS, V. PETROW, and (MISS) D. WEDLAKE.

PROLONGED treatment of 3β-hydroxypregna-5 : 16-dien-20-one (I) with potassium cyanide in boiling aqueous ethanol gave 16α-carboxy-3β-hydroxypregn-5-en-20-one, through the intermediate 16α-cyano-3β-hydroxypregn-5-en-20-one (II).

The cyano-group in the ketone (II) is assigned the α-configuration by application of the "rule of the rear." This configuration is retained by the carboxyl group formed on hydrolysis, since conversion of the 20-oxo-group of 16α-carboxy-3β-hydroxypregn-5-en-one



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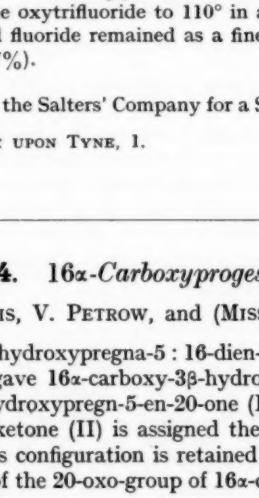

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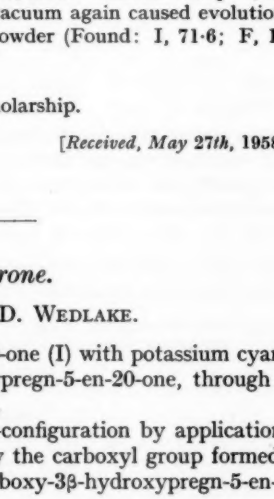

(III)

into a secondary alcohol group by reduction with sodium borohydride leads to acidic material devoid of γ-lactone properties. Molecular models indicate that γ-lactone formation is unlikely when an α-configuration of the 16-carboxyl group obtains and is unavoidable when this configuration is β.

16α-Carboxy-3β-hydroxypregn-5-en-20-one was converted into its methyl ester and thence by Oppenauer oxidation into the αβ-unsaturated ketone (III; R = Me). Saponification gave the required 16α-carboxyprogesterone (III; R = H).

Experimental.—Reaction of 3β-*hydroxypregna*-5 : 16-*dien*-20-*one with potassium cyanide.* The ketone (I) (15 g.), potassium cyanide (5 g.), ethanol (200 ml.), and water (50 ml.) were heated under reflux for 12 hr. After addition of ether (1 l.), the mixture was extracted with water (250 ml.) and the extract diluted with more water (200 ml.). Acidification to Congo-red gave a copious white precipitate which was collected, washed, and crystallised from aqueous ethanol, to give 16α-*carboxy*-3β-*hydroxypregn*-5-*en*-20-*one* (10 g.) in plates, m. p. 234—235°, $[\alpha]_D^{22}$ −113·5° (*c* 0·72) (Found: C, 73·1; H, 9·1%; equiv., 351. $C_{22}H_{32}O_4$ requires C, 73·3; H, 8·95%; equiv., 360).

In other experiments, in which the reaction period was reduced to 2—3 hr., the neutral fraction contained two nitrogenous compounds, one readily soluble and the other very sparingly soluble in ether. The former compound was purified from aqueous ethanol, to give 16α-*cyano*-3β-*hydroxypregn*-5-*en*-20-*one*, needles, m. p. 229—231°, $[\alpha]_D^{20}$ +3° (*c* 1·41) (Found: C, 77·1; H, 9·1; N, 4·3. $C_{22}H_{31}O_2N$ requires C, 77·4; H, 9·15; N, 4·1%). Prolonged hydrolysis of this with aqueous-ethanolic potassium hydroxide gave 16α-carboxy-3β-hydroxypregn-5-en-20-one, m. p. and mixed m. p. 234°. Treatment of the nitrile with acetic anhydride–pyridine at 100° gave the 3β-*acetate*, needles (from aqueous ethanol), m. p. 197—199°, $[\alpha]_D^{22}$ −2·5° (*c* 1·02) (Found: C, 75·3; H, 8·7. $C_{24}H_{33}O_3N$ requires C, 75·2; H, 8·65%).

The second sparingly-soluble reaction product, m. p. *ca.* 260°, proved difficult to purify. It was acetylated in pyridine at 100° to give (probably) 3β-*acetoxy*-16α-*carbamoylpregn*-5-*en*-20-*one*, needles (from acetone–hexane), m. p. 215—217° (Found: C, 71·3, 71·0; H, 8·7, 8·9. $C_{24}H_{35}O_4N$ requires C, 71·8; H, 8·6%).

Reduction of 16α-*carboxy*-3β-*hydroxypregn*-5-*en*-20-*one.* The carboxylic acid (3·6 g.) in methanol (100 ml.) was treated with sodium hydroxide (0·5 g.) in water (10 ml.), and then with sodium borohydride (1·5 g.). After 2½ hr. at room temperature, the mixture was acidified with acetic acid and carefully diluted until solid was no longer precipitated. The product was collected, washed, and dried at 100° to give material (3·4 g.) with m. p. 240—245°. This was very sparingly soluble in most organic solvents and could not be satisfactorily recrystallised. Titration with alkali gave equiv. 372 ($C_{22}H_{34}O_4$ requires equiv., 362). The infrared spectrum (for which we are indebted to Mr. M. T. Davies, B.Sc.), determined in Nujol suspension, revealed bands at 3411 and 3230 cm.$^{-1}$, corresponding to two differently situated hydroxyl groups. A broad band at 1686 cm.$^{-1}$ confirmed the presence of the carboxyl group.

3β-*Hydroxy*-16α-*methoxycarbonylpregn*-5-*en*-20-*one*, prepared from the acid by treatment with hot methanolic hydrogen chloride, crystallised from methanol in needles, m. p. 208°, $[\alpha]_D^{23}$ −112·5° (*c* 1·03) (Found: C, 73·7; H, 9·0. $C_{23}H_{34}O_4$ requires C, 73·7; H, 9·0%).

16α-*Methoxycarbonylprogesterone.* A solution of the foregoing ester (4 g.) in toluene (200 ml.) and *cyclo*hexanone (40 ml.) was distilled until 50 ml. of distillate had collected. After addition of aluminium *iso*propoxide (2·5 g.) in toluene (10 ml.), the mixture was refluxed for 2 hr., cooled, and washed with dilute sulphuric acid, then with water, and the solvents were removed by steam-distillation. The solid product was purified from aqueous methanol to give the *ester* as needles, m. p. 153—154°, $[\alpha]_D^{20}$ +12·5° (*c* 1·12) (Found: C, 74·0; H, 8·6. $C_{23}H_{32}O_4$ requires C, 74·15; H, 8·7%).

16α-*Carboxyprogesterone*, prepared from this ester by hot aqueous-methanolic potassium hydroxide, separated from aqueous methanol in plates, m. p. 250—255°, $[\alpha]_D^{20}$ +9·5° (*c* 1·2), $\lambda_{max.}$ 240 mμ (log ε 4·23) (Found: C, 72·9; H, 8·4; equiv., 360. $C_{22}H_{30}O_4$ requires C, 73·7; H, 8·4; equiv., 358). [α] refer to chloroform solutions.

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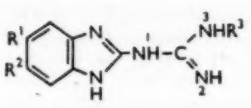
765. *The Synthesis of Some Benziminazoles.*

By R. M. Acheson, G. A. Taylor, and Muriel L. Tomlinson.

Several years ago a number of benziminazoles, structurally similar to "Paludrine," were synthesised [1] in the hope that they might have antimalarial properties or shed some light on the mode of action of "Paludrine" itself. Only one ($R^1 = R^2 = Cl$, $R^3 = Pr^i$ of the benziminazoles showed even slight antimalarial activity. Nevertheless, on screening as antibacterials the compounds containing chlorine showed considerable activity against a virulent human type of *M. tuberculosis* grown in Dubos medium containing "Tween 80" (0·01%) and bovine albumin (0·2%). It was therefore of interest to synthesise other benziminazoles of the same type as potential chemotherapeuticals, and disappointing to find that none of the chloro-compounds ($R^1 = Cl$, $R^2 = H$, $R^3 = H$, Et, or Pr^i; $R^1 = R^2 = Cl$, $R^3 = H$, Me, Et, or Pr^i) showed appreciable activity against the H37Rv strain of *M. tuberculosis* in mice.



R^1	R^2	R^3	Activity *	R^1	R^2	R^3	Activity *
Me	H	Pr^i	4	Me	H	H	5
MeO	MeO	Pr^i	1	H	H	H	1
Cl	Cl	Pr^i	100	Cl	H	H	5
Me	Me	Pr^i	5	MeO	H	H	2
Cl	H	Pr^i	20				

* Max. dilution (10^{-4} ml./g.) for complete inhibition of growth.

From the screening *in vitro* it was clear that the chlorinated derivatives were the most promising as antituberculosis agents. Several more were therefore synthesised from the appropriate *o*-phenylenediamines and the dicyandiamides, and purified *via* the picrates in the usual way.[1] No difficulties were encountered except in attempts to combine *tert.*-butyldicyandiamide with 1 : 2-diamino-4 : 5-dichlorobenzene; here the original diamine was recovered as the picrate in over 70% yield and none of the desired product was obtained. The failure may be due to steric effects of the *tert.*-butyl group as *n*-butyldicyandiamide behaves normally in the condensation.[1]

1 : 2-Diamino-4 : 5-dichlorobenzene has been obtained [1] by a somewhat fickle catalytic hydrogenation of the corresponding dinitro-compound which is also not easy to prepare in quantity.[2] Reduction of the dinitro-compound with hydrazine hydrate in the presence of Raney nickel [3] gave poor yields of the diamine. An alternative synthesis was achieved through the hydrogenation of 1-amino-4 : 5-dichloro-2-nitrobenzene which had already been obtained by two methods.[4] In the shorter of these 2 : 4 : 5-trichloronitrobenzene was treated with ethanolic ammonia at 200°, and similar reactions with aliphatic amines have been described.[5] Re-investigation of the ammonia reaction showed that much charring took place at 200°, at 140—150° both the chlorine atoms activated by the nitro-group were replaced, yielding 1 : 5-diamino-4-chloro-2-nitrobenzene as the main product, while at 115° 1-amino-4 : 5-dichloro-2-nitrobenzene was obtained with minimum contamination.

Experimental.—*5-Chloro-2-(N³-ethylguanidino)benziminazole.* 4-Chloro-*o*-phenylenediamine dihydrochloride, obtained from 4-chloro-2-nitroaniline (34·6 g.) in the usual way,[1] was refluxed with ethyldicyandiamide (25·5 g.) in water (90 ml.) for 45 min. After treatment with charcoal the filtrate and washings were added to picric acid (42 g.) in boiling water (1·1 l.), the *benziminazole picrate* (80·4 g.), m. p. 225° (decomp.), being precipitated. It was collected, refluxed with just sufficient ethanol to form a paste, cooled, and collected again (59·7 g.; m. p. 235°). Further recrystallisation from ethanol–water (3 : 1 v/v) gave a yellow powder, m. p. 245°

[1] Acheson, King, and Spensley, *Nature*, 1947, **160**, 53; *J.*, 1948, 1366.
[2] Acheson and Taylor, *J.*, 1956, 4727.
[3] Brown and Nelson, *J. Amer. Chem. Soc.*, 1954, **76**, 5149.
[4] Beilstein and Kurbatow, *Annalen*, 1879, **196**, 221.
[5] Barlow and Ing., *J.*, 1950, 713.

(Found: C, 41·1; H, 3·1; Cl. 6·9. $C_{10}H_{12}N_5Cl,2C_6H_3O_7N_3$ requires C, 41·1; H, 3·2; Cl, 7·6%). The partially purified picrate (59·2 g.), mostly dissolved in hot ethylene glycol monomethyl ether (75 ml.), was treated with propan-1-ol (70 ml.) containing hydrogen chloride (13·9 g.). After a few moments precipitation of the *benziminazole dihydrochloride* was assisted by the addition of dry ether (1 l.). The hydrochloride [36·2 g.; m. p. 190—195° (decomp.)] was well washed with dry ether to remove picric acid and was purified by dissolution in propan-1-ol, treatment with charcoal, and precipitation by propanol containing hydrogen chloride (20%). The colourless crystalline product had m. p. 192—194° (decomp.) (Found: C, 37·1; H, 5·0; Cl, 32·1. $C_{10}H_{12}N_5Cl,2HCl,H_2O$ requires C, 36·6; H, 4·9; Cl, 32·4%).

5 : 6-*Dichloro*-2-(N³-*methylguanidino*)*benziminazole*. 1 : 2-Diamino-4 : 5-dichlorobenzene (30 g.), methyldicyandiamide (20 g.), concentrated hydrochloric acid (60 ml.), and water (120 ml.) were refluxed for 1 hr. and poured into excess of 2N-sodium hydroxide. The yellow precipitate was washed with water, dissolved in a mixture of concentrated hydrochloric acid (40 ml.), water (100 ml.), and ethanol (100 ml.), and filtered into a hot solution of picric acid (40 g.) in water–ethanol (300 ml. + 100 ml.). The precipitated picrate was extracted twice with 50% aqueous ethanol (100 ml., 80 ml.) and converted into the *dihydrochloride* in 2-ethoxyethanol–tetrahydrofuran (4 : 1). It separated from aqueous methanol containing hydrogen chloride in fine needles, m. p. 263—265° (decomp.) (Found: C, 32·9; H, 3·5; N, 21·3. $C_9H_9N_6Cl_2,2HCl$ requires C, 32·6; H, 3·3; N, 21·2%). The *base*, precipitated from the aqueous dihydrochloride by ammonia, had m. p. 244° (Found: C, 42·3; H, 3·6; N, 27·3. $C_9H_9N_5Cl_2$ requires C, 41·9; H, 3·5; N, 27·1%).

5 : 6-*Dichloro*-2-(N³-*ethylguanidino*)*benziminazole*. This was prepared similarly by using ethyldicyandiamide; the *hydrochloride* separated from water in pale brown needles, m. p. 259—260° (Found: C, 38·5; H, 4·2; N, 22·6. $C_{10}H_{11}N_5Cl_2,HCl$ requires C, 38·9; H, 3·9; N, 22·7%).

5 : 6-*Dichloro*-2-(N³-iso*propylguanidino*)*benziminazole*. This was obtained as the *hydrochloride hemihydrate* from methanolic hydrochloric acid and had m. p. 206—211° (decomp.) (Found: C, 39·5; H, 4·6; N, 21·1. $C_{11}H_{13}N_5Cl_2,HCl,\frac{1}{2}H_2O$ requires C, 39·8; H, 4·5; N, 21·1%).

tert.-*Butyldicyandiamide*. *tert.*-Butylamine hydrochloride (111 g.) and sodium dicyandiamide (90 g.) were refluxed in butan-1-ol (600 ml.) for 24 hr. Filtration followed by evaporation *in vacuo* gave the *dicyandiamide* (130 g.) which separated from aqueous ethanol as colourless waxy crystals, m. p. 188—189° (decomp.) (Found: C, 51·4; H, 8·6. $C_6H_{12}N_4$ requires C, 51·4; H, 8·6%).

Methyldicyandiamide [6] was basic enough to form a *hydrochloride*, m. p. 161—163° (decomp.), which crystallised from water (Found: C, 21·4; H, 6·8; N, 33·2. $C_3H_6N_4,HCl,2H_2O$ requires C, 21·1; H, 6·5; N, 32·9%). Ethyldicyandiamide [1,6] formed a *picrate* which separated from water as a yellow powder, m. p. 204—205° (decomp.) (Found: C, 33·6; H, 3·7; N, 27·3. $C_4H_8N_4,C_6H_3O_7N_3,H_2O$ requires C, 33·4; H, 3·6; N, 27·3%).

1 : 2 : 4-*Trichloro*-5-*nitrobenzene*.[7] Nitric acid (110 ml.; *d* 1·42) was added dropwise (30 min.) to a stirred mixture of 1 : 2 : 4-trichlorobenzene (159 ml.) and concentrated sulphuric acid (455 ml.) originally at 40°, the temperature being kept below 70°. After an additional 30 min. at 60° the hot mixture was poured into water (3 l.). The precipitate was washed with water and on recrystallisation from ethanol (200 ml.) gave the nitro-compound (304 g., 84%) as pale yellow needles, m. p. 58·5°.

1-*Amino*-4 : 5-*dichloro*-2-*nitrobenzene*. (i) 1 : 2 : 4-Trichloro-5-nitrobenzene (150 g.), ethanol (250 ml.), and aqueous ammonia (500 ml.; *d* 0·880) were heated in a rotating autoclave at 115° ± 3° for 4½ hr. The solid product (113 g.) was collected, dried, and recrystallised from water (300 ml.)–acetone (600 ml.), the nitroamine forming orange needles (62 g.), m. p. 173—174°, raised to 175·5° on recrystallisation from acetic acid. The acetyl derivative, prepared by boiling acetic anhydride, separated from acetic acid in yellow needles, m. p. 123·5°.

Attempts to decrease the losses during purification of the crude material were unsuccessful. The solubilities of the monoamine and the contaminating diamine do not differ greatly, and mixed crystals are produced from most solvents.

When the ammonolysis was carried out at 140—153° the product (largely 1 : 5-diamino-4-chloro-2-nitrobenzene), after precipitation with water, had m. p. 178° depressed to 156—160°

[6] Hendry, Kenny, Murray, and Rose, *J.*, 1948, 1630.

[7] Holleman and van Haeften, *Rec. Trav. chim.*, 1921, **40**, 67, mention this preparation without giving details.

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on mixture with 1-amino-4 : 5-dichloro-2-nitrobenzene. Refluxing with acetic anhydride containing a trace of sulphuric acid gave probably 1 : 5-diacetamido-4-chloro-2-nitrobenzene, which crystallised from acetic acid as a yellow powder, m. p. 238·5° (Found: C, 44·0; H, 3·7; N, 15·4. Calc. for $C_{10}H_{10}O_4N_3Cl$: C, 44·2; H, 3·7; N, 15·5%). " About 222° " is the m. p. given [8] for the chlorination product of 1 : 3-diacetamido-4-nitrobenzene.

(ii) 1 : 2-Dichloro-4 : 5-dinitrobenzene (0·5 g.) was heated and stirred rapidly with urea (1·0 g.) on an oil-bath. At *ca.* 160° two layers were formed, much gas was evolved, and after a few minutes the deep red mixture became homogeneous. The solid obtained on cooling crystallised from methanol; the least soluble fraction, the amine, separated in yellow needles, m. p. 178° (Found: C, 34·9; H, 1·9; N, 13·1. Calc. for $C_6H_4O_2N_2Cl_2$: C, 34·8; H, 1·9; N, 13·5%) (lit.,[9] m. p. 176°).

1 : 2-*Diamino*-4 : 5-*dichlorobenzene.* (i) 1-Amino-4 : 5-dichloro-2-nitrobenzene (20 g.) was hydrogenated (5 atm.) over Raney nickel in tetrahydrofuran (80 ml.) at room temperature. After filtration the solution was diluted with water, the diamine (16 g.) being precipitated. After recrystallisation from light petroleum (b. p. 100—120°) it had m. p. 161°. (ii) A solution of 100% hydrazine hydrate (20 ml.) in methanol (20 ml.) was added to one of 1 : 2-dichloro-4 : 5-dinitrobenzene (1·0 g.) in methanol (20 ml.) to which Raney nickel had been added. Then the mixture was heated on a water-bath for 10 min., by which time the solution was grey. The mixture was concentrated to a small volume and water (50 ml.) was added. The precipitate was collected and extracted with hot benzene, and the extract evaporated to dryness. The residue on recrystallisation from benzene and light petroleum gave grey crystals of the diamine (0·33 g., 45%), m. p. 161°. The *picrate* separated from aqueous ethanol in yellow needles, m. p. 182—184° (decomp.) (Found: C, 35·6; H, 2·1. $C_6H_6N_2Cl_2,C_6H_3O_7N_3$ requires C, 35·5; H, 2·2%). The *dibenzenesulphonyl derivative*, prepared in the usual way in pyridine, separated from acetic acid in colourless needles, m. p. 196—197° (Found: C, 47·6; H, 3·0. $C_{18}H_{14}O_4N_2Cl_2S_2$ requires C, 47·3; H, 3·1%) (lit.,[10] m. p. 186°). The diamine (0·14 g.) also reacted with pyrene-1 : 2-quinone (0·17 g.) in hot acetic acid, yielding 6 : 7-*dichloropyreno*(4′ : 5′-2 : 3)*quinoxaline* which was precipitated by water. It separated from acetic acid (600 ml.) in yellow needles (0·18 g.), m. p. 297° (Found: C, 70·6; H, 2·9. $C_{22}H_{10}N_2Cl_2$ requires C, 70·8; H, 2·7%).

We thank Dr. E. Schlittler, of Ciba Pharmaceuticals Inc., for arranging the *in vivo* tests, Dr. C. N. Iland for the *in vitro* data, and Mr. A. O. Plunkett for some technical assistance.

THE DYSON PERRINS LABORATORY, and THE DEPARTMENT OF BIOCHEMISTRY,
OXFORD UNIVERSITY. [*Received, June 4th*, 1958.]

[8] Morgan and Wootton, *J.*, 1905, **87**, 935.
[9] Blanksma, *Rec. Trav. chim.*, 1902, **21**, 420.
[10] Adams and Winnick, *J. Amer. Chem. Soc.*, 1951, **73**, 5687.

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766. *The Melting Points of* cis- *and* trans-cyclo*Hexane*-1 : 2-*diol Di*-p-*nitrobenzoates.*

By T. H. ELLIOTT.

THE recorded [1] melting points are 128—128·5° and 149—150°, respectively, but these should be transposed.

*cis-cyclo*Hexane-1 : 2-diol [2] gave a di-*p*-nitrobenzoate, m. p. 149° (Found: C, 58·1; H, 4·4; N, 6·5. Calc. for $C_{20}H_{16}O_8N_2$: C, 58·0; H, 4·4; N, 6·8%), and a 3 : 5-dinitrobenzoate, m. p. 169° (lit.,[1] 169°).

The *trans*-diol [3] gave a di-*p*-nitrobenzoate, m. p. 129—129·5° (Found: C, 58·4; H, 4·5; N, 6·5%), and a 3 : 5-dinitrobenzoate, m. p. 179° (lit.,[1] 179°).

Each ester was hydrolysed by alkali to the parent diol.

DEPT. OF PHARMACEUTICS, UNIVERSITY OF MALAYA. [*Received, May 9th*, 1958.]

[1] Wilson and Read, *J.*, 1935, 1269.
[2] Vogel, " A Textbook of Practical Organic Chemistry," 2nd Edn., 1954, p. 895.
[3] Roebuck and Adkins, *Org. Synth.*, Coll. Vol. III, 1955, p. 217.

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